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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1951

ORIGINAL ARTICLES

PREVENTION OF DEGENERATIVE VASCULAR LESIONS IN YOUNG PATIENTS BY CONTROL OF DIABETES*†

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THE prevention of premature vascular disease in diabetes mellitus of long duration is today the most important and challenging problem in the management of patients with this disease. It is now generally recognized that as long as treatment with diet and insulin is adequate enough to prevent definite symptoms and acidosis, patients usually do well for several years after onset. However, after 10, 15, or 20 years of diabetes an alarmingly high proportion show retinitis and generalized arteriosclerosis. The resulting complications including impaired vision, coronary heart disease, diabetic nephropathy, and peripheral vascular disease are all the more distressing when they occur in young patients in their 30's or 40's at a time of life when, if they were not diabetic, they might expect to be healthy, vigorous, and essentially free of vascular disease.

The cause of these degenerative complications has been a matter of great concern to all interested in diabetes. In recent years some have regarded premature vascular disease as inevitable and related to the duration of diabetes and possibly to an unidentified "X" factor[10]. Some have advocated, therefore, a program of management in which a "free diet" is allowed and insulin given only to the extent of preventing acidosis and actual symptoms[4, 6, 9, 16-18]. In this plan, glycosuria and

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hyperglycemia are disregarded as long as acidosis is not present. It is argued that this type of management is easier and that under it patients lead more nearly normal lives and are disturbed less emotionally and psychologically[19].

Opposed to this point of view have been those, including the writers and their associates, who believe that every effort should be made to restore physiological conditions, including freedom from glycosuria and a normal blood sugar, insofar as this is practicable[3,11, 13]. Proponents of this plan of consistent vigorous treatment believe that, for the most part, the degenerative complications of diabetes are related directly to inadequately controlled diabetes[7a,14,15, 20]. A restricted though entirely adequate diet is insisted upon and treatment with insulin pursued as vigorously as possible without producing frequent hypoglycemic attacks.

It is obvious that there is an urgent need for reliable facts which will help decide as to whether treatment of diabetes generally should be along the lines of the "free diet" with less regard for hyperglycemia, or in accordance with a program of vigorous treatment with careful continuous control. Unfortunately, to acquire worthwhile data is not easy. Persons whose onset of diabetes is after the age of 40 are not suitable subjects, because after 20 years they are at an age at which vascular disease is common anyway and it is difficult to assess the part played by diabetes. Among younger persons with onset of diabetes under the age of 30, the number available for study after 20 years of diabetes has until recently been too small to warrant conclusions. Furthermore, over 20 years of time so many factors, personal and environmental, enter into an individual's life that it is difficult to set up 2 comparable study groups, one with and the other without good control of diabetes. Finally, and of extreme importance, is the fact that the diabetic condition of no patient is perfectly controlled over 20 years of time, in the sense that the urine is always free from sugar and the blood sugar oscillates within a normal range. One deals perforce with individuals whose diabetes has been under varying degrees of inadequate control. One speaks of the best of these as having good or excellent control, but in so doing it must be realized that even in these there may well be over years of time definite effects of the disturbed metabolism of diabetes.

In this study we have attempted to correlate the degree of control of diabetes maintained by patients over a period of many years with the incidence and severity of degenerative complications in the arteries, kidneys, heart, and retinae.

Material and Method. For this purpose, we have studied a group of 247 patients whose diabetes began between the ages of 18 months and 30 years, and whose diabetes had been in existence for no less than 10 years and for periods varying from 10 years up to 34 years.

Every patient included in this survey has been recalled for review and observation either to the New England Deaconess Hospital or to our office where the necessary studies and laboratory procedures could be conducted. It should be emphasized that no questionnaire was sent out for patients to fill in themselves. Patients reported in the fasting state before either breakfast or insulin had been taken.

After a specimen was voided for urinalysis, 30 cc. of venous blood were withdrawn, dye was injected intravenously for the phenolsulfonphthalein excretion test, and insulin was administered. The patients were then allowed to have breakfast. Urine specimens were collected at intervals of 30 minutes, 1 hour, and 2 hours following the phenolsulfonphthalein dye injections. During the periods between these collections the remainder of the laboratory procedures was completed, a physical examination was done, and an interview was held with each person to elicit an interval history since his last visit and to obtain the data needed to evaluate properly the type of treatment and the degree of control which the individual had maintained. The results of these studies together with a summary of pre-

vious examinations in the office or hospital were tabulated on a special form which provided space for information relative to occupation, education, family history, pregnancy, complicating illnesses, insulin dosage, and diet formula, in addition to the results of laboratory procedures.

Among the various laboratory tests which were completed in each case were the following:

Examination was made by a roentgenologist for evidences of calcification within the blood vessels on films taken of the pelvis, lower legs, and the abdominal aorta (lateral film). (It is worthy of emphasis that many films taken by Roentgen-ray technicians will fail to disclose slight traces of calcium within the arteries which become evident on films which are correctly taken.) A film of the chest for measurement of heart size was done on every person.

An electrocardiogram recording the 3 standard leads plus the augmented unipolar extremity and 6 precordial leads was done in each case.

Determinations of the index of capillary fragility were done in each case, utilizing a modification of the Göthlin technique in which pressure equivalent to 80 mm. of mercury was maintained for 4 minutes and the petechiae counted in a 6-cm. circle along the flexor surface of the forearm, as described by Barnes[2].

Examination of the eyes by certified ophthalmologists included tonometer measurement of intraocular tension, tests for visual fields and acuity, slit-lamp examinations, and both direct and indirect ophthalmoscopy. In many of the cases color photographs of the retinae were taken. All funduscopic examinations were done after dilating the pupils and the objective findings were classified as follows:

NORMAL FUNDI: No hemorrhages, exudates, sclerosis, or other abnormal changes seen.

GRADE I: Few tiny petechial hemorrhages or micro-aneurysms seen scattered about one or both retinae. No exudates seen.

GRADE II: Several petechial hemorrhages and/or micro-aneurysms seen in both fundi. A few to many small hard white and/or soft white exudates bilaterally.

GRADE III: Many petechial aneurysms and/or hemorrhages bilaterally. Some splinter hemorrhages also seen in deep and superficial layers of retina. Many exudates scattered about both retinae.

GRADE IV: Severe advanced retinitis of proliferative type (retinitis proliferans), retinal detachment, acute or chronic hemorrhagic glaucoma.

Renal function was evaluated by determinations of phenolsulfonphthalein excretion, urea clearance, microscopic examination of the urine sediment, and quantitative measurement of proteinuria (using 2% sulphosalicylic acid and the technique of Kingsbury, Clark, Williams, and Post[8]).

The blood chemical studies done in each case were the determination of fat and protein and their fractions, including total lipids; phospholipid; free, esterified, and total cholesterol; total serum protein, albumin, and globulin. Blood erythrocyte and leukocyte counts and hemoglobin determinations were also done routinely.

Simple but fairly rigid standards of control were established. The tabulated summary of each patient's clinical and laboratory data both at home and under medical observation was compared with these standards. The actual results achieved by each patient from his endeavors to control his diabetes were determined by careful scrutiny of the many records from previous office or hospital visits, and in addition by direct questioning during the personal interviews in this study. Each patient was then classified according to the type of treatment and degree of control followed in the management of his diabetes. Those considered to have maintained Excellent, Good or Fair Control must have fulfilled all the criteria listed for the respective classification. Furthermore, any patient to whom any or all of the criteria of Poor Control could be properly applied was considered as having Poor Control.

Standards of Control. EXCELLENT CONTROL: 1. Patient must never have been in coma. 2. Insulin was begun within a few weeks of the onset of diabetes. 3. Urine tests for sugar made more than once daily ever since onset of diabetes with conscientious attempt to have the urine sugar-free or nearly so before meals. Insulin dosage adjustments determined by results of urine tests. 4. Diet must have been weighed for at least 80% of the duration since onset of symptoms of diabetes. 5. Regular physical examination and laboratory tests by a physician must have been faithfully completed at least once annually. Blood and urine tests satisfactory.

GOOD CONTROL: 1. Patient must never have been in coma except in those instances in which the initial diagnosis of diabetes was made in coma. 2. Insulin was begun within a few weeks after the onset of diabetes. 3. Urine tests for sugar made at least once daily ever since onset of diabetes with conscientious attempt to have the urine sugar-free or nearly

so before meals. Insulin dosage adjustments were made according to results of urine tests. 4. Diet must have been weighed for the first 6 weeks of treatment and thereafter at intervals with careful measurement of food at all other times since onset of diabetes. 5. Regular physical examination and laboratory tests by a physician at least once annually. Blood and urine tests satisfactory.

FAIR CONTROL: 1. Patient must never have been in coma (except for cases in which the diagnosis was made with the patient in coma, or rare cases in which an unavoidable overwhelming infection or other complication precipitated coma). 2. Insulin begun within 24 months of onset of symptoms of diabetes. 3. Tests of the urine for sugar were made with a frequency of once or more times weekly in an attempt to have sugar-free urine tests. 4. Dietary management by the patient must have been conscientiously attempted, although food was not weighed or measured. Rarely, if ever, indulged in gross dietary indiscretions. 5. Satisfactory blood sugar determination made at the time of physical examinations by the patient's doctor at least once every 2 years.

POOR CONTROL: 1. Avoidable coma one or more times. 2. Insulin not begun until more than 24 months after onset of diabetes and in some cases taken irregularly. 3. Urine specimens tested infrequently, or at intervals of months or years. 4. No measurement or weighing of food in relation to urine tests or insulin dosage. 5. No regular examinations by a physician. At long intervals, office or hospital examination showed marked glycosuria and hyperglycemia.

Results. As shown in Table 1, only 7 patients could be classified as maintaining Excellent Control, and 30 as achieving Good Control. A total of 37 patients (nearly 15%) thus made up the Good and Excellent groups. The Fair Control group numbered 51 patients (20.7%), while Poor Control had been maintained by 159 patients (64.4%).

TABLE 1.—DISTRIBUTION OF PATIENTS ACCORDING TO DEGREE OF CONTROL OF DIABETES

	Cases	
Control	*Number*	*%*
Excellent	7	2.8
Good	30	12.1
Fair	51	20.7
Poor	159	64.4
	247	100

Among the 37 patients of the Excellent and Good groups, 3 patients were found to whom the Quarter Century Victory Medal was awarded. This Medal is offered to any diabetic patient anywhere in the world who, after having diabetes for 25 years, can be shown by roentgenographic examinations of the leg and pelvic arteries, a lateral film of the aorta, and a chest film to be free from any evidence of calcification of the vessels. The fundi examined by a certified ophthalmologist must be free from hemorrhages, exudates, or other lesions. The blood pressure must be normal and the urine free from albumin. Already 23 such patients have received the medal, of whom 10 are from our own practice. (See summary of findings reported by Joslin[7b].)

ONSET AND DURATION. Table 2 summarizes the age at onset of diabetes. Seventeen patients developed diabetes under 5 years of age and 44 between the ages of 5 and 15. In 166 patients diabetes began between 15 and 25 years of age.

It was observed that, although these cases were later grouped according to the degree of control of diabetes maintained, each of the groups was comparable with the others as regards age at onset of diabetes.

TABLE 2.—DISTRIBUTION OF CASES ACCORDING TO AGE AT ONSET OF DIABETES

	Cases		
		Group	
Ages in years	*Number*	*Total*	*%*
1.5 to 4	17		
5 to 9	13	61	24.8
10 to 14	31		
15 to 19	100		
20 to 24	66	166	67.1
25 to 30	20	20	8.1
	247	247	100

In Table 3 it is seen that 86 patients had diabetes for 10 to 15 years, 58 patients from 15 to 20 years, and 103

patients had diabetes which had been present from 20 to 34 years. In only 1 patient had diabetes been present for 34 years.

Among the 103 patients who had diabetes for 20 to 34 years, there were 30 whose age at onset was less than 15 years, 66 who developed diabetes between the ages of 15 and 25 years, and 7 in whom the disease began between the ages of 25 and 30 years. This group of long duration cases thus includes a representative sample of all age groups.

TABLE 3.—DISTRIBUTION OF CASES ACCORDING TO DURATION OF DIABETES

	Cases	
Duration in years	*Number*	*%*
10 to 15	86	34.4
15 to 20	58	24.7
20 and more	103	41.9
	247	100

INSULIN DOSAGE. In Table 4 the patients are grouped according to daily insulin dosage. Criteria of the severity of diabetes are not entirely satisfactory, but none seemed more applicable to this group of patients than the insulin dosage. It may be said that all such youthful patients do have essentially severe diabetes. Only 35 of the patients in this study took less than 30 units of insulin daily; in 170 cases the dose was between 30 and 70 units; the remaining 45 patients took between 70 and 120 units of insulin daily. Only 13% of the patients in the Excellent and Good groups took less than 30 units of insulin daily. These were therefore not the cases with the mildest degree of diabetes.

SEX AND HEREDITY. As shown in Table 5 the sexes were equally divided, as is in general true of the sex distribution of diabetes in early life, there being 122 male and 125 female patients in the group. It is only in the diabetes of middle age that the dominance of the female sex becomes manifest.

TABLE 4.—CORRELATION BETWEEN SEVERITY OF DIABETES AND DEGREE OF CONTROL

	Degree of control				
Insulin Units daily	*Excellent*	*Good*	*Fair*	*Poor*	*Number of cases*
8 to 30	0	5	4	26	35
31 to 70	7	20	38	105	170
71 to 110	0	5	7	28	40
over 110	0	0	2	0	2
	7	30	51	159	247

There was a history of diabetes in the relatives of 133 of these patients at the time of the present examination, an incidence of 54%. This high incidence is attributed to the long duration over which many of these patients have been followed.

TABLE 5.—CORRELATION BETWEEN CONTROL OF DIABETES AND DISTRIBUTION OF CASES ACCORDING TO SEX

	Sex	
Degree of control	*Male*	*Female*
Excellent	2	5
Good	16	14
Fair	28	23
Poor	76	83
	122	125

SOCIAL STATUS. The educational achievements and occupational status of the entire group of 247 patients are summarized in Tables 6 and 7. Considering the entire population of the United States, 15.9% of persons are high school graduates, but only 3.1% have graduated from college[25]. Among the patients seen during this study, 188 patients (72%) were high school graduates, while 44 patients (18%) had gained college degrees. These statements acquire increased significance when viewed in the light of the unnecessary wastage of these intellectually superior individuals as a result of inadequately treated diabetes.

PREGNANCY. Sixty-one of the 125 female patients had been pregnant a

TABLE 6.—DISTRIBUTION OF CASES ACCORDING TO EDUCATIONAL ACHIEVEMENT

Formal education discontinued	*Number of cases*
Below sixth grade	3
Below high school	17
During high school	39
Graduated from high school	68
Beyond high school	63
Graduated from college	24
Beyond college	20
Unknown	13
	247

TABLE 7.—DISTRIBUTION OF CASES ACCORDING TO OCCUPATION AND SEX

Occupational status	*Number of cases*
Full time employment	224
Part time employment	9
Unable to work	14
	247

Type of work done by the 233 patients able to work	*Sex*	
	Female	*Male*
Housework	63	—
Student	4	3
Professional	1	7
Skilled work	31	48
Semi-skilled work	15	29
Unskilled work	7	25
	121	112

TABLE 8.—RESULTS OF 114 PREGNANCIES AMONG 61 OF THE FEMALE PATIENTS IN THIS GROUP

		Number of cases
Pregnancy	114	
Abortion		9
Miscarriage		21
Stillbirth		16
Live birth		68
Neo-natal death	6	
Deliveries	84	
Pelvic		43
Cæsarean		41
Sex	84	
Male		43
Female		41
Hormone Therapy	30	

total of 114 times. The outcome of the pregnancies is as charted in Table 8. Among 32 patients who had hormone therapy (stilbestrol and progesterone) during pregnancy there resulted 26 live births with 1 neo-natal death.

COMPLICATIONS. It is often extremely difficult to determine in a diabetic patient whether a specific condition is truly a complication of diabetes or whether it represents merely a co-existing condition unrelated to diabetes. This becomes less of a problem among the young diabetic patients especially when considering premature degenerative vascular complications. Table 9 reveals the relative frequency with which complicating conditions were observed in association with diabetes among the 247 patients examined. Certain of these conditions are seen only in the presence of diabetes, while others listed are much less specific for diabetes.

Among the 122 males examined in this study, calcification of the vas deferens was found to be present in 17. This unique condition has been observed in 60 patients seen at this hospital recently and is believed to be a degenerative complication seen particularly among diabetic patients[22].

Thirteen patients who were examined during the course of this study have died since examination. In all these fatal cases, death occurred before the age of 41 and was primarily the result of diabetic nephropathy. Postmortem examinations were done in 9 of these cases. The clinicopathological findings are to be summarized in a separate paper[24].

FUNDI. It must be admitted that calcification is often a rather late manifestation of vascular disease. Certainly increased capillary fragility has come to be regarded as an earlier evidence of vascular disease and is frequently found elevated long before other

changes appear. However, roentgenologic evidence of vascular calcification is objective and is surprisingly closely correlated with changes in the fundi. In Table 10 is summarized the correlation between the minimal, moderate, and marked degrees of vascular calcification and funduscopic findings. In order to define these degrees of vascular calcification it should be said that the word "minimal" was applied to patients in whom one or more specks of calcium were visible in linear arrangement in 1 or 2 small areas not over 1 or 2 cm. in length, while the remainder of the arteries of the lower leg, the pelvis, and the aorta were free. "Moderate" calcification indicated tiny areas of calcification arranged in linear form with parallel order for distances of more than 1 or 2 cm. in 1 or more arteries. "Marked" indicated dense calcification

TABLE 9.—FREQUENCY OF OCCURRENCE OF CONDITIONS COMPLICATING DIABETES IN 247 PATIENTS

Complication	*Number of cases*	*Complication*	*Number of cases*
Calcified vessels	164	Necrobiosis lipoidica diabeticorum	10
Retinitis	158	Osteomyelitis	8
Coma	69	Gangrene	7
Nephropathy	62	Insulin lipodystrophy	7
Hypertension	48	Cataracts	6
Retinitis proliferans	26	Impotence	6
Pyelonephritis	24	Allergy	5
Calcified vas deferens	17	Epilepsy	4
Neuritis	15	Hepatomegaly	2
Frequent severe hypoglycemia	13	Retarded growth	2
Tuberculosis	12	Neuropathic feet	1
Chronic diarrhea	11		

TABLE 10.—CORRELATION OF THE EXTENT OF VASCULAR CALCIFICATION WITH RESULTS OF FUNDUSCOPIC EXAMINATIONS FOR VARIOUS DURATIONS OF DIABETES IN 247 CASES

		Degree of Vascular Calcification								
		Minimal			Moderate			Marked		
Funduscopic examination	*Number of patients*	*Duration of diabetes in years*			*Duration of diabetes in years*			*Duration of diabetes in years*		
		20+	*15–20*	*10–15*	*20+*	*15–20*	*10–15*	*20+*	*15–20*	*10–15*
Normal	89	17	13	35	16	4	2	2	0	0
Grade 1 Only a few tiny hemorrhages	46	9	9	16	5	2	3	1	1	0
Grade 2 Moderate number of hemorrhages and some exudates	56	10	8	13	11	6	5	2	1	0
Grade 3 Many deep and superficial hemorrhages and many exudates	30	3	1	7	6	5	2	6	0	0
Grade 4 Retinitis proliferans and most marked retinitis	26	2	4	1	6	4	2	7	0	0
	247	41	35	72	44	21	14	18	2	0
			148			79			20	

in arteries and their branches in the legs, pelvis, or aorta.

In 89 patients normal fundi were observed. Only 6 patients of this group with less than 20 years of diabetes showed moderate or marked degree of vascular calcification, while in 65 patients of this group minimal calcification was found. Forty-six patients showed Grade 1 funduscopic findings. These included only a few tiny red areas which may be either tiny hemorrhages or aneursymal dilatations as described by Ballantyne[1]. It is impossible to say that these tiny lesions will progress. Certainly in some instances they have remained constant without progression for many years. Again it should be noted that only 2 of the 46 patients of this group showed marked calcification. Minimal and moderate calcification occurred in the remaining 44 patients. With Grade 2 and Grade 3 retinitis a moderate number to many deep and superficial hemorrhages and exudates were seen in a total of 86 patients. Here again, marked calcification was not seen except in 9 instances in which diabetes had been present for more than 20 years. Grade 4 retinitis included retinitis proliferans and most extensive retinitis and was seen in 26 patients.

Correlation between the capillary fragility index and the funduscopic examination is tabulated in Table 11. It is shown that 58 of the 76 patients with normal capillary fragility index had normal or only minimal fundus changes, while of the 23 patients with Grade 4 retinitis 18 showed increased fragility.

CONTROL. The most striking evidence of the extreme importance of the factor of control is illustrated by tables 12 through 15. The entire group of 247 patients has been analyzed in Tables 12 and 13 to correlate the degree of control of diabetes maintained with the incidence of vascular calcification and retinitis observed. Among all patients who had maintained better than Fair Control, only 9 showed more than minimal vascular calcification and only 7 showed more than minimal retinitis.

It may be pointed out that a consid-

TABLE 11.—CORRELATION OF RESULTS IN 216 CASES IN WHICH CAPILLARY FRAGILITY TESTS AND FUNDUSCOPIC EXAMINATIONS WERE CARRIED OUT

	Funduscopic examination	*Number of patients*	*Capillary fragility index*			
			Normal 0–10 petechiæ	*Grade I 10–50 petechiæ*	*Grade II 50–200 petechiæ*	*Grade III 200 plus petechiæ*
MINIMAL	NORMAL	78	44	16	16	2
	GRADE I Only a few tiny hemorrhages	41	14	11	10	6
MODERATE	GRADE II Moderate number of hemorrhages and some exudates	44	6	13	10	15
	GRADE III Many deep and superficial hemorrhages and exudates	30	7	5	9	9
MARKED	GRADE IV Retinitis proliferans and most marked retinitis	23	5	4	7	7
		216	76	49	52	39

TABLE 12.—CORRELATION OF THE DEGREE OF CONTROL WITH INCIDENCE OF VASCULAR CALCIFICATION SEEN IN THE TOTAL GROUP OF 247 PATIENTS

Degree of control	*Vascular calcification*			*Number of cases*
	Minimal	*Moderate*	*Marked*	
Excellent	5	2	0	7
Good	23	7	0	30
Fair	31	16	4	51
Poor	89	54	16	159
	148	79	20	247

TABLE 13.—CORRELATION OF THE DEGREE OF CONTROL WITH INCIDENCE OF RETINITIS SEEN IN THE TOTAL GROUP OF 247 PATIENTS

Degree of control	*Retinitis*			*Number of cases*
	Minimal	*Moderate*	*Marked*	
Excellent	7	0	0	7
Good	23	7	0	30
Fair	31	15	5	51
Poor	73	65	21	159
	134	87	26	247

TABLE 14.—CORRELATION OF THE DEGREE OF CONTROL WITH INCIDENCE OF VASCULAR CALCIFICATION SEEN IN THE 103 PATIENTS HAVING HAD DIABETES MORE THAN 20 YEARS

Degree of control	*Vascular calcification*				*Number of cases*
	Normal	*Minimal*	*Moderate*	*Marked*	
Excellent	1	1	2	0	4
Good	8	6	5	0	19
Fair	4	7	8	3	22
Poor	4	10	29	15	58
	17	24	44	18	103

TABLE 15.—CORRELATION OF THE DEGREE OF CONTROL WITH INCIDENCE OF RETINITIS SEEN IN THE 103 PATIENTS HAVING HAD DIABETES MORE THAN 20 YEARS

Degree of control	*Retinitis*				*Number of cases*
	Normal	*Minimal*	*Moderate*	*Marked*	
Excellent	3	1	0	0	4
Good	10	4	5	0	19
Fair	9	4	6	3	22
Poor	12	6	28	12	58
	34	15	39	15	103

erable number of patients under Poor Control had minimal vascular calcification (89 cases or 56%) and minimal retinal changes (73 cases or 46%); however, the majority of these cases were of only 10 years' duration. After 20 or more years of poorly controlled diabetes the incidence of minimal vascular lesions decreases markedly, as shown in Tables 14 and 15. This illustrates how, with an increase in the duration of diabetes, the factor of control acquires increasingly greater importance[23].

Among 103 patients, all of whom had diabetes mellitus for more than 20 years (Tables 14 and 15), thereby rendering the factor of duration a constant, it can be seen that of the 4 patients who maintained Excellent Control none showed marked calcification of blood vessels or retinitis; of the 18 patients with marked vascular calcification 15 had Poor Control; and of the 15 with marked retinitis 12 showed Poor Control.

Furthermore, among the 80 patients who maintained Poor or Fair Control (living on an unmeasured diet without constant use of insulin and without constant control of glycosuria) for periods of at least 20 years, 55 (69%) showed advanced vascular calcification, and 49 (61%) had severe retinitis.

Thus, while duration is important, it must be emphasized that careful control of the disease over the years seems to be more important than any other factor in preventing or postponing the degenerative complications of diabetes.

It is worth noting that 63% of the patients who maintained Good or Excellent Control were among those with diabetes of more than 20 years' duration, whereas only 38% of the cases with Poor or Fair Control had diabetes for 20 or more years. Thus, it seems not unreasonable to conclude that careful control and aggressive treatment of diabetes may prolong life as well as prevent the severe degenerative complications in these young patients.

Lipids. The ratio of cholesterol to phospholipid in blood plasma was determined because of the recent emphasis upon this relationship as an important factor in precipitation of lipids in vascular tissue[5,12]. The distribution of these values within and above the normal zone requires interpretation together with other lipid values and the protein fractions, which is reserved for a separate communication[21]. Analysis of renal function and pathology also will be reported later[24].

Summary. A group of 247 patients whose diabetes began between the ages of 18 months and 30 years and had been in existence for a minimum of 10 years to a maximum of 34 years have been studied extensively and with particular emphasis upon the relationship between control of the diabetes and the development of degenerative lesions in the kidneys, retinae, and blood vessels.

Ideal or perfect control of diabetes implies that a diet planned to provide proper amounts of minerals, vitamins, and calories derived from a proper proportion of carbohydrate, protein, and fat has been so well utilized by means of an adequate insulin effect that blood and urine tests are invariably normal. Simple standards of control (Excellent, Good, Fair, and Poor), less rigid than ideal and defined in the test have been applied to this group. When various degrees of control and lack of control were plotted against the duration of diabetes and the development of calcified vessels, retinitis, and albuminuria, the following facts appeared in these 247 patients:

1. No patients with Excellent or Good Control showed advanced calcification or retinitis even after periods of 20 to 34 years of diabetes.

2. No case of diabetic nephropathy developed in patients with Good or Excellent Control, even after periods of 20 to 34 years of diabetes. Sixty-two

patients having maintained Poor or Fair Control developed diabetic nephropathy, among whom 13 died during the year of this study.

3. In 89 patients (one-third of the entire number) no retinal hemorrhage or retinitis was present. This group included 35 patients with diabetes of more than 20 years' duration.

4. In 103 patients with diabetes for periods of at least 20 years and a maximum of 34 years, 3 of the 4 cases with Excellent Control had no retinal lesions. Of 54 with moderate to marked retinitis, all but 5 had had Fair or Poor Control, and none Excellent Control.

5. Fifty-five patients among 80 cases who lived for periods of at least 20 years (under Poor or Fair Control) on an unmeasured diet, without constant use of insulin and without constant control of glycosuria, showed severe degenerative lesions (calcified arteries, retinitis, or nephropathy).

6. Whatever the specific etiologic factors causing diabetic degenerative lesions may be (endocrine, infectious, or metabolic), it is demonstrated that the regulation of diabetes controls these factors. Control of diabetes is thus more important than any known factor such as duration or severity in preventing these degenerative complications.

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INCIDENCE OF DIABETIC RETINOPATHY RELATIVE TO THE DEGREE OF DIABETIC CONTROL

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The increased liability of diabetics to develop retinal vascular disease is well known. In 1947, Dolger[4] reported that 100% of 200 patients with diabetes up to 25 years' duration developed retinal hemorrhages, regardless of age of onset, severity of disease, or method of treatment. White[13] found that 80% of her young diabetics (200 patients) exhibited retinal hemorrhages after 20 years of diabetes. She felt there was less retinopathy in the better controlled diabetics. Jackson[7,8] and his group, in studying over 170 juvenile patients with diabetes of at least 10 years' duration, believe a significant relationship exists between the level of diabetic control and the development of retinal hemorrhages.

For physician and patient alike, it is important to determine, if possible, whether there is any causative relationship between the degree of control of the diabetes and the appearance and extent of the retinal changes. It was to add further evidence on this subject that the present study was undertaken.

One difficulty encountered in attempting to study this problem was to define "good control" of the diabetes. Dillon and Dyer[3] believe that good control consists of normal blood sugar values, minimal glycosuria, maintenance of ideal weight, and freedom from hypoglycemic attacks. Similarly strict criteria have been proposed by Joslin[9], Palmer[10], and Jackson[8]. White[13] considered the incidence of acidosis, extreme hyperglycemia, hypercholesterolemia, and hepatomegaly as her criteria of poor diabetic control. Tolstoi[11] believes that patients should be symptom-free, maintain optimal weight, have an acetone-free urine on a dose of insulin, if necessary, and be economically and socially well adapted. If these be present, he considers the patient satisfactorily controlled, irrespective of glycosuria or hyperglycemia.

Regardless of what criteria are chosen to define good control, the dynamic ever-changing nature of diabetes makes difficult the determination as to whether a patient's disease has been well or poorly controlled over a period of several years.

Material and Criteria. The material used in this study consists of 50 cases from the Diabetic Clinic of the Hospital of the Univer-

sity of Pennsylvania. The basis for selection was diabetes of at least 10 years' duration. An attempt was made to select patients who have attended clinic for the total duration of their diabetes. This was possible in 47 cases. In the remaining 3 cases, the patients were observed for at least 50% of their known diabetic period. Beginning August 1, 1949, the first 50 such cases encountered fulfilling the criteria mentioned above, now attending clinic, were chosen for this study.

The average age of the entire group was 58 years. There were 38 women and 12 men. The duration of diabetes varied from 10 years to more than 25 years. Included in the group were 7 juvenile-type diabetics with the onset of diabetes before the age of 20.

A thorough review of each patient's protocol was made and various features were noted. These included their insulin dosage, the duration of diabetes, and the occurrence of diabetic acidosis. All the urine sugar reports (0 to 4+) appearing on the charts were tabulated and scored in a manner to be described below.

If each of the 4 fractional urine specimens presented by the patient at each clinic visit contained 4+ sugar (over 1%) using Benedict's Reagent, the maximum score possible at each clinic visit would be 16 (namely, 4 x 4). Any fraction thereof would be representative of the degree of control relative to glycosuria. Hence a patient with 1+ (½%) sugar in each specimen would receive a score of 4 (1 x 4) or, expressed in percentage of the maximum of 16, $4/16 = 25\%$. For the purposes of this study we define "well controlled diabetics" as those having an overall "glycosuria score" of 25% or less for the entire period of observation. This scoring is not applicable to those patients with an altered renal threshold. The "glycosuria score" and the incidence of diabetic acidosis were the only factors considered in determining the degree of diabetic control.

We realize that this method might have many shortcomings, but it is one possible approach to a difficult problem. There are 2 patients in the series who have a high renal threshold. One of these has refused to take insulin and has had hyperglycemia (over 250 mg. per 100 cc.) at every clinic visit. The other patient, although receiving insulin, has maintained a blood sugar over 250 mg. for the majority of clinic visits. These 2 cases are included in the poorly controlled group, despite an apparently good "glycosuria score."

Not every patient presented in this series has had an annual funduscopic examination. For this reason we cannot draw any conclusions as to just when in the course of the disease the retinopathy occurred. Rather, we are concerned with the frequency of diabetic retinopathy in the "well controlled diabetic" compared with similar changes in the "poorly controlled diabetic", both groups having diabetes for the same length of time.

Although there has been disagreement as to the specificity of diabetic retinopathy, more and more observers have come to feel that a characteristic fundus picture does exist[1,5,12]. All patients were examined under mydriasis and a diagnosis of diabetic retinopathy was confirmed to those showing punctate hemorrhages (that is, aneurysmal capillary dilatations, as has been pointed out by Ballantyne[2] and more recently by Friedenwald[6]). Concomitant findings were waxy yellow exudates and flame-shaped or vitreous hemorrhages.

Results. Of the entire group of 50 patients, 25 have a "glycosuria score" of under 25%. None of these patients has had diabetic acidosis. The remaining 25 patients have a "glycosuria score" of over 25%, and 9 of these have had at least 1 episode of diabetic acidosis. This latter group of 25 patients has been classified as "poorly controlled diabetics". Seventeen of these 25 patients (68%) have diabetic retinopathy. This is in contrast to the "well controlled" group where 4 of the 25 patients (16%) have diabetic retinopathy.

The average age of the "poorly controlled" group is 56 years and the "well controlled" group 63 years. The average age of the "poorly controlled" group with retinopathy is 58 years and that of the "well controlled" group with retinopathy is 54 years.

The average amount of insulin taken by the patients in this series is different in the 2 groups. It is not surprising that the "poorly controlled" group has larger insulin doses. Significant is the observation that the insulin dosages are approximately the same with or without retinopathy in each group (Table 1). This is in agreement with most observers who believe the amount of insulin taken bears no relation to the incidence of retinal changes.

TABLE 1.—THE RELATIONSHIPS BETWEEN INSULIN DOSE (UNITS 24 HOURS), DIABETIC CONTROL AND RETINOPATHY IN 50 PATIENTS; SHOWING THAT THE INSULIN DOSAGE PER DAY IS ROUGHLY SIMILAR IN THE TOTAL GROUP AND IN THE GROUP WITH RETINOPATHY

Control	*Average insulin dose units/24 hours all patients*	*Average insulin dose units/24 hours patients with retinopathy*
Poor	49	39
Good	20	23

TABLE 2.—INCIDENCE OF RETINOPATHY IN 9 PATIENTS WHO HAVE HAD AT LEAST 1 HOSPITAL ADMISSION FOR ACIDOSIS; SHOWING THE HIGH INCIDENCE OF RETINOPATHY IN PATIENTS WHO HAVE HAD ACIDOSIS

Patient	*"Glycosuria score"*	*Hospital admissions for acidosis*	*Duration of diabetes years*	*Retinopathy*
J. N.	33	1	12	+
P. S.	26	1	12	+
B. B.	35	2	15	+
N. O.	55	1	17	0
M. E.	35	1	22	+
N. C.	51	1	22	+
R. H.	35	2	24	0
C. C.	—	2	25	0
M. V. G.	30	2	27	+

TABLE 3.—RELATION OF DIABETIC CONTROL, DURATION OF DIABETES AND INCIDENCE OF RETINOPATHY, SHOWING A MUCH HIGHER INCIDENCE OF RETINOPATHY IN THOSE CASES CLASSED AS "POORLY CONTROLLED" BY THE CRITERIA RECORDED IN THE TEXT

Duration of diabetes years	*Well controlled*		*Poorly controlled*	
	No. of pts.	*Retinopathy*	*No. of pts.*	*Retinopathy*
10–15	13	3 (23%)	11	8 (73%)
16–20	9	1 (11%)	5	2 (40%)
21–on	3	0 (0%)	9	7 (78%)
TOTAL	25	4 (16%)	25	17 (68%)

TABLE 4.—COMPARISON OF DIABETIC CONTROL IN HOSPITAL AND CLINIC IN THE 15 OF OUR GROUP OF 50 DIABETICS WHO WERE ADMITTED TO THE HOSPITAL AT SOME TIME DURING THEIR COURSE FOR STANDARDIZATION OF THEIR DIABETES

Patient	*"Glycosuria score" in clinic*	*Insulin dose in clinic*	*"Glycosuria score" in hospital*	*Insulin dose in hospital*	*Retinopathy*
P. P.	40	(20)-0-0-0	5	(10)-0-0-0	+
N. C.	51	(30)-10-0-0	18	(30)-10-0-0	+
K. M.	62	(30)-20-0-0	5	(30)-5-0-0	+
J. T.	52	(35)-0-0-0	20	(40)-20-0-0	+
N. O.	55	(36)-24-0-12	5	(36)-20-0-12	0
J. N.	33	(25)-0-0-0	5	(25)-0-0-0	+
M. S.	41	(25)-0-0-0	5	(20)-0-0-0	+
Y. S.	22	(28)-0-0-0	11	(28)-0-0-0	0
M. F.	12	(15)-0-0-0	5	(15)-0-0-0	0
S. C.	12	0	5	0	+
R. W.	12	(15)-0-0-0	17	(20)-0-0-0	+
C. H.	7	0	0	0	0
P. S.	10	(20)-0-0-0	5	(20)-0-0-0	+
A. R.	33	(30)-20-0-0	5	(20)-0-0-0	0
M. R.	34	(40)-0-0-0	36	(20)-10-0-0	+

Of the 9 patients who have experienced at least 1 episode of diabetic acidosis, 6 patients (67%) have retinal lesions (Table 2).

Table 3 and Fig. 1 show the relationship between the degree of diabetic control, the duration of the diabetes, and the incidence of retinopathy. Note that 9 of 14 "poorly controlled" patients have retinal changes after 16 or more years of diabetes, but only 1 of 12 "well controlled" patients has retinal changes after the same duration of diabetes.

The question arises as to whether the patients who are "poorly controlled" according to the "glycosuria score" may not be more severe diabetics and that the "severity of the diabetes", rather than the "poor control", was responsible for the development of retinal hemorrhages. To study this question, the hospital records of those patients in this group admitted for diabetic standardization were reviewed. The "glycosuria score" and insulin dose during hospitalization were compared with the overall "glycosuria score" and insulin dose in the clinic (Table 4). Fifteen such cases in this series were hospitalized for standardization, and are available for comparison. Of the 9 patients who were considered "poorly controlled" as out-patients, all but 1 were considered well controlled when on a strict hospital regimen of diet and insulin. As out-patients, however, they have had persistently heavy glycosuria.

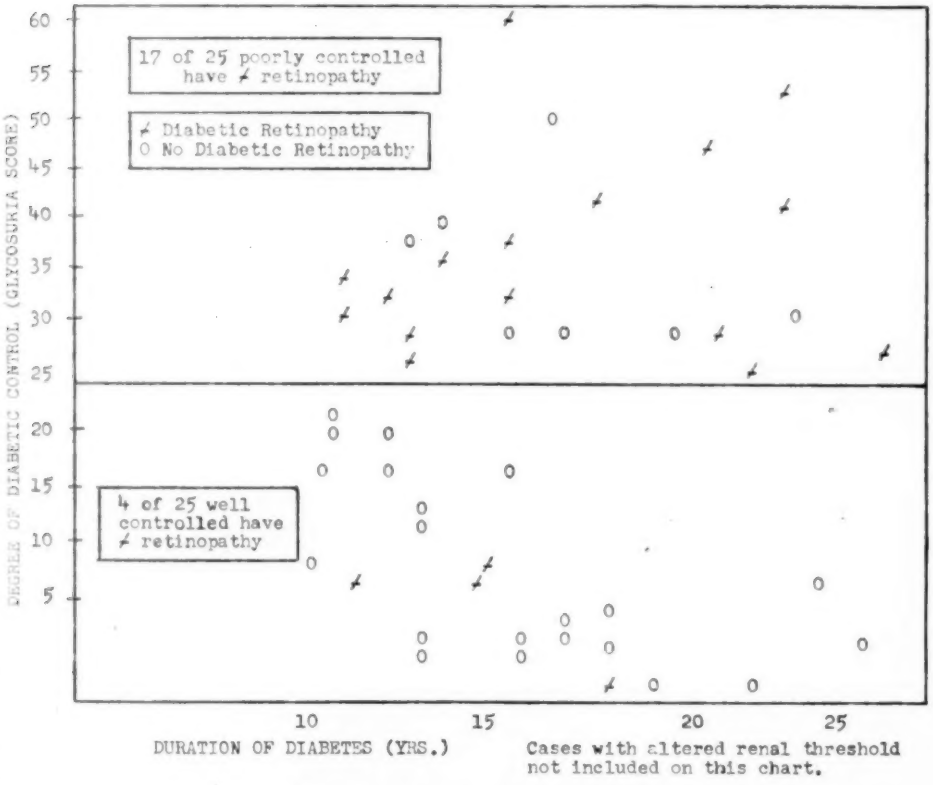

FIG. 1.—Relation of retinopathy to duration and control of diabetes mellitus.

Although these data are not absolutely conclusive, they would imply that such patients are not more severe diabetics but are "poorly controlled" as out-patients because of lack of adherence to the prescribed diet and insulin program.

Summary and Conclusions. 1. A group of 50 patients with diabetes of at least 10 years' duration has been studied in an effort to determine the relationship between diabetic control and the incidence of diabetic retinopathy.

2. Evaluation of the degree of diabetic control is difficult.

3. Criteria used to differentiate good control from poor control of the diabetes include the degree of glycosuria for the entire known duration of the diabetes, and the occurrence of diabetic acidosis.

4. There is a significantly greater incidence of retinal lesions in the group classed as "poorly controlled" diabetic patients in this series, as compared with the "well controlled" group.

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IATROGENIC HYPOTHYROIDISM*†

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The title of this paper is a little misleading. In most instances I do not believe physicians actually render patients permanently myxedematous with the use of thyroid therapy. It has been pointed out by Farquarson[2], however, that the use of thyroid extract does inhibit the production of normal thyroid secretion in non-myxedematous patients with hypometabolism. What I would like to imply is that many physicians although they do not organically suppress thyroid secretion permanently with thyroid extract, do, however, very frequently give patients whose basal metabolic rates are low the impression that their thyroid glands are functioning poorly. This impression is often a lasting one, and the patient, therefore, feels not only condemned, but actually eager to take thyroid for life. If these people are not in a permanent state of hypothyroidism, they certainly think that they are.

Who are these people who seem so temptingly amenable to simple hormonal mismanagement? They are people we all see. They make up a very large part of the internist's practice, especially his private practice. They are mostly females, and to a certain extent they can be fairly well grouped.

In the first place, there are those who are obese.

In the second place, there are those in adolescence who are either obese though menstruating, or who are thin and not menstruating, or who are both obese and not menstruating.

Thirdly, there is the group of young ladies who have finished school or college or who have accomplished a debut and who are biding their time awaiting the next exciting step in life which they think ideally is marriage.

Next is the group of young ladies who having attained the state of ideal marital excitement find it actually not so exciting to be saddled with household chores, children and a tired, quarrelsome, mostly absent husband.

The old adage about pastures appearing greener on the other side of the fence applies to the next group: the ladies who feel they have passed the marrying age without marrying. Far from profiting from the experience of their hypometabolic married sisters, they also seem to decline into a hypometabolic state.

In reviewing these groups individually and collectively for a moment, it is not difficult to see that probably a common denominator is a state of frustration. Under these circumstances the administration of thyroid is a stop gap at best, usually unsuccessful, unless accompanied by large doses of understanding interest in each girl's

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problem and associated with the presence or development of insight on the part of both the patient and the physician. In the presence of such a fortuitous coincidence, thyroid need never be administered to patients falling in one of these groups.

The obese woman obviously eats more than she burns. She should therefore, either eat less or burn more, or both. Of course it is not quite as simple as Newburgh[6] would lead us to believe, however, because behind the bulk of each obese person stands a psychological problem which must be unravelled before satisfactory reduction occurs. An interested physician can probably accomplish this better without thyroid extract. If he cannot, thyroid extract will be only temporarily helpful.

The nonmenstruating fat adolescent will probably menstruate satisfactorily, if she is going to, merely with careful observation. If she doesn't something more complicated than hypothyroidism will probably be discovered to be her difficulty.

My interest in the next group, those girls who are marking time with bated breath between debut and wedding bells, dates back to house officer days. A friend reported to me with interest that 7 of her friends, one after the other, were being given thyroid by their physicians. They were tired and run down and needed pep. It seemed rather incredible to me at the time that they could all have incipient myxedema. During the course of the next 10 years I have followed the progress of these girls, some professionally and some socially. All discontinued thyroid at the time of their marriage, all have had children, and now all are fast joining the next group which comprises the hypometabolic young housewives. It has been very difficult to keep those who are under my care away from thyroid substance.

There are many other conditions for which thyroid is used seemingly on a completely empirical basis. Cave[1] states in a recent article on the treatment of chronic subdeltoid bursitis: "The internist should review the patient generally and possibly prescribe thyroid or other hormones which in some instances appear to be effective." Greenblatt[3], discussing the management of uterine bleeding, states: "Thyroid therapy should be administered to all patients with normal or subnormal basal metabolic rate."

Thyroid is used in treating sterility in otherwise apparently normal women. It is also administered with other hormones to control threatened abortion. No one can be certain of its efficacy under either of these circumstances.

It would be foolish universally to decry the use of thyroid in the treatment of all patients who do not have myxedema, especially if there is any doubt as to whether it might be helpful. On the other hand it should be used by the physician in all honesty on a trial basis. The patient should be taken into his confidence to the extent that he or she will not forever lose respect for his or her own thyroid secretions.

The following histories are those of 4 patients who, though probably normal, were made thyroid addicts by their physicians.

Case Reports. CASE 1. Patient A (Fig. 1) was a fat 16 when she first began taking thyroid 5 grains daily. She lived in a very small town where her widowed mother was the telephone operator. In spite of this large amount of thyroid, it was not until her second year in college at the age of 19 that an appreciable weight reduction and increase in basal metabolic rate were apparent. She remained in *status quo* until 1944 when she went to New Guinea with the Red Cross and for 6 months did well without thyroid therapy. A severe bombing caused a state of exhaustion. She was evacuated to Australia where her basal metabolic

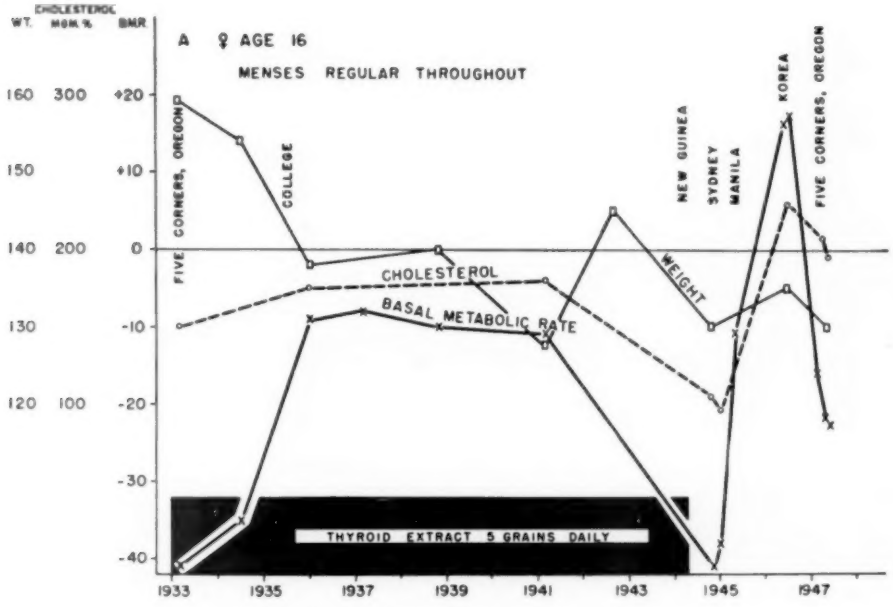

FIG. 1.—Significant Data in Patient A.

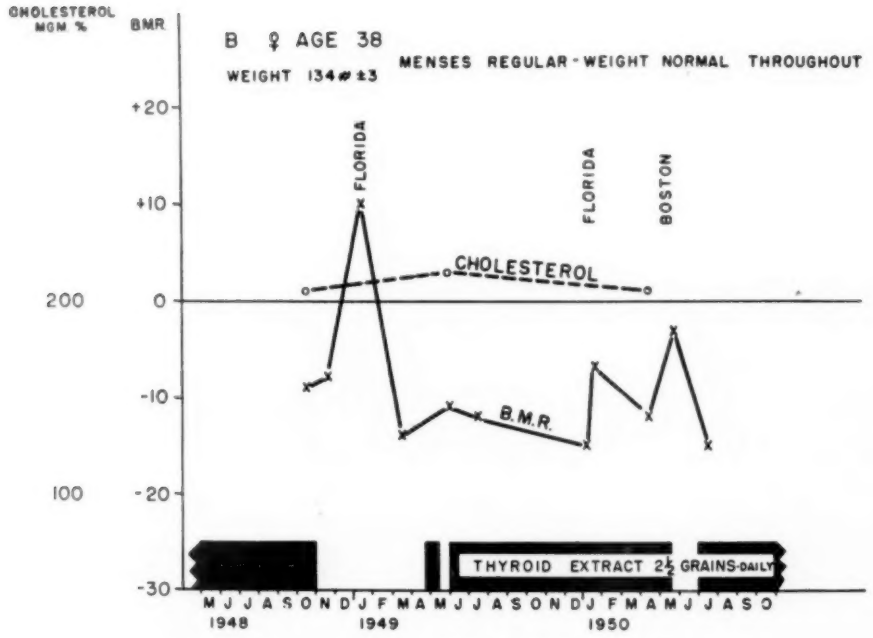

FIG. 2.—Significant Data in Patient B.

rate was found to be low, but serum cholesterol levels were 101 and 98 mg. per 100 cc. No thyroid was prescribed, she was allowed to rest and then encouraged to lead a normal social life. In Manila 4 months later, her basal metabolic rate was −11%. In Korea in 1946 holding a responsible administrative position, her basal metabolic rate was +17%. After the war she returned to her very small home town. She remained there a year, less and less inspired, hampered by her mother. Her basal metabolic rate fell to −16%. She was examined at Vanderbilt University Hospital where she was found to be normal with basal matabolic rate of −22 and −23%. No thyroid was prescribed. She went to New York. In a follow-up communication from her (date October, 1950) she stated she was fine. Weight and menses were normal, and she had not bothered to have her basal metabolic rate determinations repeated.

Case 2. Patient B (Fig. 2) was 38 when first seen at Vanderbilt University Hospital. She had been taking thyroid 2½ grains daily for 15 years. She had had 5 children, the oldest 17 years, the youngest 8 years. She was born and reared in New England and never accustomed herself to the softer, slower southern life. She worked Puritanically hard, raising her children, expected strict hard work of those around her, and had no close female friends. Although possessed of far more energy than are most housewives, it irritated her to be tired. She took thyroid unsuccessfully to prevent fatigue and because she had been told that her low basal metabolic rate was responsible for the fatigue. She had been told she was somewhat anemic and bought her own hemoglobinometer to keep track of this. When seen at Vanderbilt University Hospital she was found to be normal. Fig. 2 is self-explanatory. When her basal metabolic rate was determined in Boston or Florida where she "relaxed", the values were somewhat higher. It was impossible to wean her from thyroid.

Case 3. Patient C (Fig. 3) was obese when she was 20 years old, and although she was apparently otherwise normal and her menstrual periods were regular, her basal metabolic rate was −16%. Thyroid, 4 grains daily, was prescribed with no change in the clinical picture. She was majoring in social psychology at college, and was the subject of one of her professor's published papers regarding individuals with low basal metabolic rate and normal menstruation. She did not begin to lose weight until 1944 when by her own admission she became more satisfied, met her future husband and shortly thereafter became engaged and was married. She then had 5 successive miscarriages, followed finally by a successful pregnancy. She discontinued thyroid therapy at the end of the 1st trimester. Her child nursed satisfactorily for 8 months. She began to take thyroid again after about 1 year's abstinence. Although when seen at Vanderbilt University Hospital in 1950 she appeared normal and no evidence of hypothyroidism was discovered, it was impossible to wean her from thyroid. When a trial period without thyroid was suggested she changed physicians.

Case 4. Patient D (Fig. 4) was a gangly boy of 15 years when he began to take thyroid, 3 grains a day. He had matured satisfactorily physically but was thought to be developing slowly intellectually. The only son of a divorcee, he had had mild chronic asthma for a number of years. He was spoiled and slightly overweight. The data in Fig. 4 were supplied by the boy's mother from notes in his baby book. Except for the fact that he grew fast and matured at an average rate intellectually, the general picture did not change appreciably. When seen at Vanderbilt University Hospital in 1949 he was a normal, tall, thin boy. He had had trouble adjusting to being away from home and was not doing too well with his studies. His mother was worried about him. All investigations including Roentgen-ray examinations of the skull were normal. His basal metabolic rate determination was low. He was weaned from thyroid, encouraged in his independence, and advised to eat a better diet and to be more regular in his habits. He has done well.

Discussion. Thyroid is administered in large quantities, in most instances unnecessarily, by physicians to patients all over the world. It is probable that patients without hypothyroidism who receive thyroid, though benefiting not at all, for the most part suffer little organic harm. While taking thyroid there is probable suppression of normal thyroid secretion which returns to normal fairly soon after thyroid is discontinued. Means[5], however, has described the development of hypermetabolism simulating precisely the picture of full blown thyrotoxicosis in a few patients

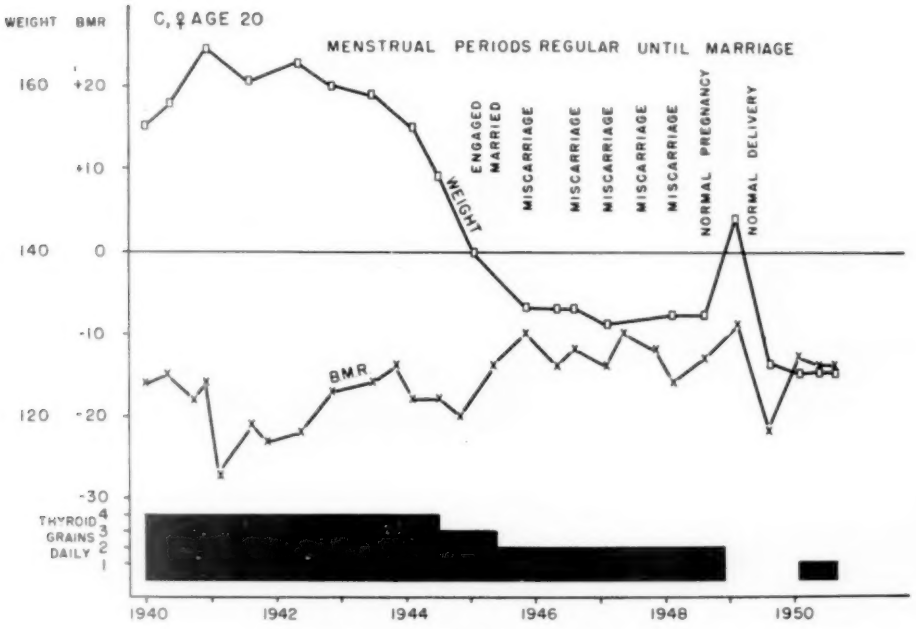

FIG. 3.—Significant Data in Patient C.

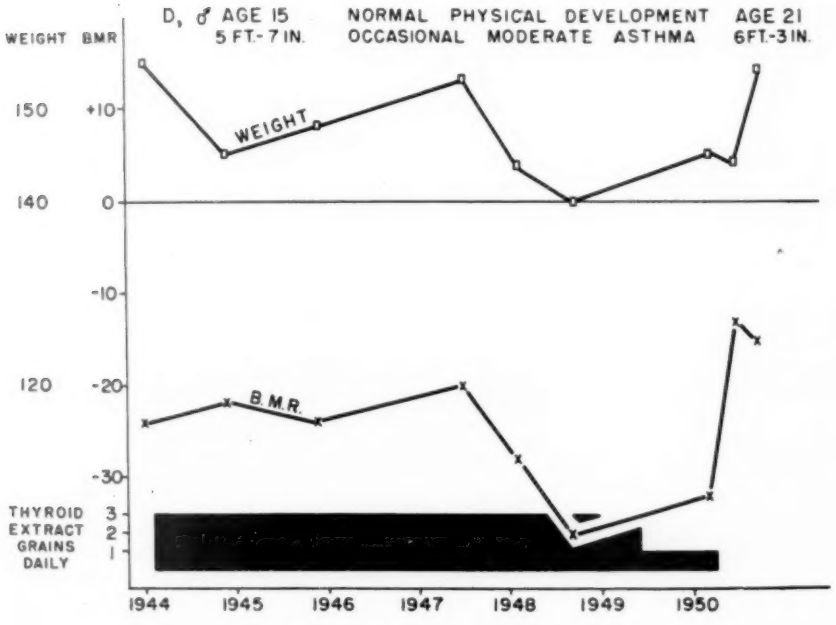

FIG. 4.—Significant Data in Patient D.

receiving large amounts of thyroid. When the medication was discontinued the hypermetabolism regressed. Levy[4] has seen cardiac auricular fibrillation occur in association with the administration of thyroid to an otherwise normal patient. The rhythm reverted to normal when this medication was discontinued.

In closing it should be re-emphasized that although there seems to be no definite proof that permanent organic change is produced in the thyroid gland by the administration of thyroid to hypometabolic people, yet these people are usually psychologically so constituted that once it is implied that thyroid under-secretion is the cause of their troubles, they might as well be myxedematous for the tenacity with which they cling to thyroid therapy.

Summary. In the light of experience, it is pointed out that thyroid administered to patients, normal except for low basal metabolic rates, probably produces no permanent organic damage. In administering thyroid under such circumstances, however, the physician usually overlooks important psychological factors. The use of thyroid to treat hypometabolism in the absence of organic hypothyroid function should be avoided.

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THE EFFECT OF CORTISONE ON THE CLINICAL COURSE OF CHRONIC REGIONAL ENTERITIS AND CHRONIC IDIOPATHIC ULCERATIVE COLITIS*

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THE purpose of this report is to present observations made when cortisone was administered to patients with chronic regional enteritis or chronic ulcerative colitis. It was thought that the compound might influence the course of the disease because of the occasional association of arthritis and of erythema nodosum.

Subjects. Three of the 6 patients (Cases 1, 2 and 3) had chronic regional enteritis, with or without involvement of the proximal colon, while the remaining 3 had typical ulcerative colitis (Table 1). Two of the latter had involvement of the entire colon (Cases 4 and 6), and one involvement of only the rectum and sigmoid (Case 5).

The duration of the disease in the 6 patients ranged from 9 to 108 months and of the episode for which Cortisone was administered, 2 to 10 months.

Most of the patients had a poor appetite, had lost weight, had an increased erythrocyte sedimentation rate and were passing numerous liquid, blood-containing stools (Table 2). Four had a low-grade fever and an equal number, varying degrees of anemia. Two (Cases 1 and 3) had acute arthritic manifestations. One patient (Case 1) was having large hemorrhages from the bowel and was in rather desperate straits. She was the most critically ill of the group; at the onset of Cortisone therapy her blood pressure could not be measured.

The Cortisone† was injected subcutaneously according to the following schedule: 100 mg. (4 cc.) every 8 hours for 3 doses, then 200 mg. (8 cc.) every 12 hours for 2 doses, and thereafter 50 mg. (2 cc.) every 12 hours for 8 additional days, the entire period of therapy lasting 10 days.

The patients were permitted access to unlimited amounts of low-residue foods; no special therapeutic measures were employed during the period of Cortisone therapy with the exception of a transfusion of a pint of blood to Case 1 who was having massive bowel hemorrhage at the time Cortisone administration was begun. It was felt unwise to withhold blood in view of her shock-like state.

Results. a) SUBJECTIVE CHANGES. Following institution of Cortisone therapy, a sense of well being was experienced by 5 of the 6 patients, the exception being Case 6. In two of them (Cases 1 and 2) this sense of well being amounted to euphoria. Appetites which had been poor became excellent; in fact, voracious in Cases 1 and 2. Joint pain and stiffness, present in 2 patients (Cases 1 and 3), disappeared within 2 days after beginning the administration of Cortisone.

b) OBJECTIVE CHANGES. 1. *Total number of eosinophils.* Following the institution of Cortisone therapy, a

* Presented before the American Clinical and Climatological Association, Stockbridge, Mass., October 16, 1950.

† Saline suspension of Cortone Acetate, Merck and Co., Inc., Rahway, N. J.

TABLE 1.—DESCRIPTION OF PATIENTS

Case	Age/Sex	Duration in months: Disease	Duration in months: Present illness	Extent of involvement
1*	16/F	12	2	Distal ileum and transv. colon
2*	38/F	108	10	Distal ileum
3	18/M	20	4	Terminal ileum and proximal ⅔ colon
4	28/F	54	3	Entire colon
5	34/M	19	3	Rectum and sigmoid
6	58/M	9	9	Entire colon

* Relapse following resection of terminal ileum and cecum.

TABLE 2.—CLINICAL AND LABORATORY CHARACTERISTICS

Case	Appetite	Loss of weight (lbs.)	Number stools per 24 hrs.	Fever	Hb. (%)	Sed. rate (mm./hr.)
1†	Poor	29 (105–76)	3–8*	+	47	33
2	Poor	42 (130–88)	10–12	0	61	32
3†	Poor	14 (117–103)	3	+	73	42
4	Fair	21 (142–121)	12–15*	0	43	28
5	Poor	20 (145–125)	4–7*	+	100	30
6	Poor	19 (162–143)	15–20*	+	99	27

* Blood present in stools.
† Also had joint symptoms.

TABLE 3.—TOTAL NUMBER OF EOSINOPHILS (PER C.MM.) BEFORE, DURING AND AFTER CORTISONE TREATMENT

Case	Before	During	After (Day)
1	70	2	175 (50)
2	69	38	63 (29)
3	237	19	113 (7)
4	225	81	156 (28)
5	275	46	118 (50)
6	1312*	38	—

* Repeat: 1060.

TABLE 4.—EFFECT OF CORTISONE THERAPY ON FEVER

Case	Before	During: 1st ½	During: 2nd ½	After
1	+	0	0	0
2	0	0	0	0
3	+	+	0	0
4	0	+	0	0
5	+	0	0	+
6	+	+	0	+

TABLE 5.—EFFECT OF CORTISONE ON NUMBER AND CHARACTER OF STOOLS

	Number of stools per 24 hours		
Case	*Before*	*During*	*At end*
1	3–8 L	0–4 F	1–3 F
2	10–12 L	1–5 F	0–3 F
3	3 S	3 F	3 F
4	12–15 L	3–9 S	0–2 F
5	4–7 L	3 F	2 F
6	15–20 L	6–18 L	8–12 L

L, liquid. S, soft. F, formed.

TABLE 6.—COURSE OF BODY WEIGHT (LBS.)

	Body weight in relation to Cortisone treatment			
Case	*Before*	*At end*	*Gain*	*2 weeks after*
1	76	94*	18	84
2	88	95	7	92
3	103	117	14	115
4	121	121	0	127
5	125	128½	3½	129
6	143	150	7	145**

* Obvious fluid retention in tissues.
** 1 week.

TABLE 7.—SEDIMENTATION RATE* BEFORE, DURING AND AFTER CORTISONE THERAPY

				After cessation of R		
Case	*Before*	*During*	*(Day)*	*1 day*	*1 week*	*2 weeks*
1	33	28	(2)	19	13	36
2	32	13	(9)	10	24	38
3	42	19	(5)	22	25	28
4	28	31	(6)	—	28	30
5	30	25	(6)	30	23	24
6	27	36	(7)	36	34	—

* Wintrobe method.

decrease in the total number of eosinophils occurred in each patient (Table 3).

2. *Fever.* A low-grade fever present in 4 of the 6 patients (Cases 1, 3, 4 and 6) prior to therapy (Table 4) disappeared during the period of Cortisone administration. It recurred in 2 of them (Cases 5 and 6) after Cortisone was discontinued.

In one patient (Case 4) fever, absent prior to therapy, developed during the first 3 days of treatment. It then disappeared and remained absent during the rest of her 17-day stay in the hospital.

3. *Diarrhea.* A change in character and number of the stools occurred in 5 of the 6 patients who manifested improvement during the period of Cortisone therapy (Table 5). This change consisted of a decrease in the number of stools, in their becoming formed and in the disappearance of gross blood when such was present. In the refractory patient (Case 6) little or no change occurred in the number and character of stools.

4. *Body Weight.* Five of the 6 patients gained weight during the period of Cortisone therapy (Table 6). This weight gain ranged from 3½ to 18 lbs.

Signs of fluid accumulation in the tissues of the retrosacral region were detected in the patient in whom the greatest weight gain (18 lbs.) occurred (Case 1). In her, a diuresis associated with loss of weight (Fig. 1) occurred following cessation of Cortisone administration.

5. *Sedimentation rate* (Table 7). A decrease in the rate of sedimentation of erythrocytes (Wintrobe method) occurred in 3 patients (Cases 1, 2 and 3). These 3 patients manifested the greatest degree of all-round improvement. The remaining 3 patients revealed no consistent trend or marked changes in sedimentation rate.

6. *Hemoglobin.* The changes in hemoglobin were inconsistent. In 3 instances (Cases 1, 2 and 4) hemoglobin

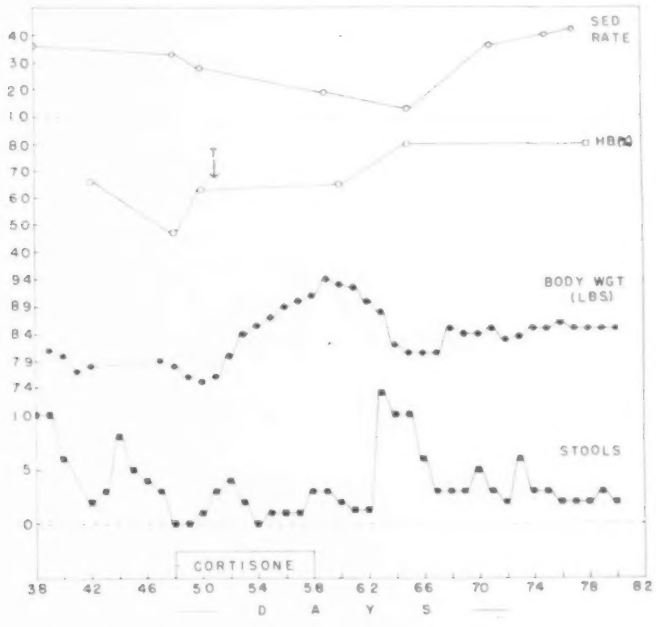

FIG. 1.—The effect of Cortisone administration on the clinical course of a patient (Case 1) critically ill with regional enteritis. During 46 days of hospitalization prior to the administration of Cortisone, she became progressively worse. She ran a low-grade fever, was anorexic, lost weight, had diarrhea, arthritic manifestations and was greatly depressed. On the 46th day the second of a series of massive bowel hemorrhages occurred. At the time Cortisone was begun her blood pressure could not be measured. Following the institution of Cortisone therapy (48th day of hospitalization) she promptly became more alert, euphoric, developed a voracious appetite, joint pains vanished, diarrhea ceased, blood disappeared from the stools, the erythrocyte sedimentation rate decreased and a gradual increase in hemoglobin percentage occurred. A transfusion of 1 pint of whole blood was administered at point (T) indicated by arrow. She gained 18 lbs. in weight, some of which was undoubtedly due to retention of fluid as, following cessation of Cortisone administration, loss of weight occurred simultaneously with a diuresis. A relapse in the diarrhea occurred 4 days after stopping Cortisone, the increase in number of stools lasted 4 days. The increased appetite continued. During the interval of improvement, several bad emotional situations were corrected: these included the finding of a new home for her illegitimate child, reassignment of the patient to another foster home where she would not be subjected to the advances of her guardian, and the promise of resumption of school by the patient with the beginning of the school term. She has continued to do well and has not relapsed during the past 9 months.

increased; in 2 (Cases 5 and 6) it decreased, and in one (Case 3) it remained essentially unchanged.

7. *Sigmoidoscopic picture.* Three of the patients (Cases 4, 5 and 6) had changes typical of ulcerative colitis visualized by means of the sigmoidoscope. In 2 of them (Cases 4 and 5) improvement in the appearance of the bowel was reported at the end of the 10-day period of Cortisone therapy. This improvement consisted of less hyperemia and edema, and less tendency of the mucosa to bleed when traumatized. Regression was observed 2 weeks later. The third patient (Case 6), who did not respond to Cortisone, was not subjected to sigmoidoscopy.

8. *Roentgen appearance of involved areas.* No significant change in the Roentgen appearance of the involved sections of diseased bowel was detected during the period of clinical improvement while on Cortisone.

c) Course Following Cortisone Therapy. A relapse occurred in each of the 5 patients who improved while Cortisone was being administered; the relapses occurred in 5 to 73 days following cessation of the treatment.

In one of the 5 (Case 1), the most critically ill of the group, the relapse was transient (Fig. 1). It occurred 5 days after cessation of Cortisone and lasted 4 days. The improvement in her clinical course which followed the institution of Cortisone therapy was prompt and dramatic, and it seemed that Cortisone was responsible for saving her life. She remains well after 9 months. The absence of a relapse during this period is attributed to the fact that the emotional factors important in the pathogenesis of her disease were successfully handled (see Fig. 1).

The remaining 4 relapsed in from 13 to 73 days after cessation of Cortisone therapy. Their emotional problems have not been successfully handled. Three of them (Cases 2, 3 and 4) have been subjected to surgery and the fourth (Case 5) probably will be. The patient (Case 6), who was refractory to Cortisone, also has been operated on.

Discussion. Moderate-to-marked remission of symptoms occurred in 5 of 6 cases of regional enteritis or colitis or both while on Cortisone therapy. Little or no improvement occurred in the sixth. In 3 of the 5 improved patients (Cases 1, 2 and 3) the improvement seemed to be definitely related to the Cortisone; in the remaining 2 (Cases 4 and 5), it may well have been, but the evidence is less clear than in the other 3. In 1 of these cases (Case 4), the clinical course (Fig. 2) was quite similar to that observed during previous admissions to the hospital when no specific treatment was administered; she did, however, manifest an increased sense of well being and increased appetite as soon as Cortisone administration was begun.

The reason why some of the patients seemed to respond to Cortisone and others did so less obviously or not at all, is not apparent at this time. The following differences between the 2 groups existed.

1) Type of Disease. Those who improved most dramatically when Cortisone therapy was instituted (Cases 1, 2 and 3) had regional enteritis with involvement of ileum with or without involvement of the proximal colon; those in whom improvement occurred, but in whom it might have occurred if Cortisone had not been administered (Cases 4 and 5), had involvement of the colon only. The involvement in Case 6, who was refractory, was also limited to the colon. In this connection it is of interest that the one good response out of 4 reported by Dearing and Brown[1] occurred in a patient with segmental colitis. Their remaining 3 patients, in whom a satisfactory response

was not obtained, had involvement of the entire colon. On the other hand, Gray and his associates[3] observed a very gratifying response following administration of ACTH in a patient with extensive involvement of the entire colon.

2) Level of Initial Total Eosinophil Count. The best responses were obtained in the 2 patients (Cases 1 and 2) who had the lowest initial total eosinophil counts (Table 3). The patient (Case 6) who had the highest eosinophil count experienced no improvement. The eosinophil counts in the 2 patients who improved but in whom the improvement may have been unrelated to Cortisone therapy, fell into an intermediate range.

3) Severity of Illness. Two (Cases 1 and 2) of the 3 patients (Cases 1, 2 and 3) who responded most dramatically were the 2 most critically ill of the group. These 2 patients also had the lowest initial total eosinophil counts. Dutoit[2] who treated 2 cases of chronic ulcerative colitis with Adrenocorticotropic hormone also observed prompt improvement in the more acutely and severely ill of his 2 patients, while there was some question as to whether or not the less critically ill patient was at all benefited. That the severity of the illness appears to be, at least at present, one of the factors which determines when a good response will be obtained is also suggested by the metabolic studies of Posey and Bargen[4]. These authors surveyed 44 patients with chronic ulcerative colitis and found widespread metabolic disturbances which became progressively more severe with increasing gravity of the disease. Urinary

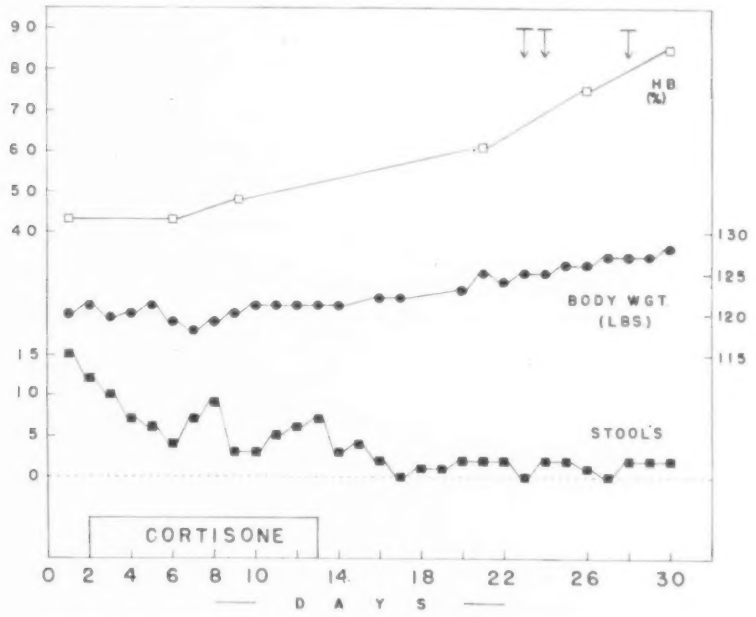

Fig. 2.—Illustrates the course of Case 4 in whom improvement occurred during Cortisone therapy but in whom it was not certain that similar improvement would have occurred without Cortisone. The reason for uncertainty is that the patient had been observed to improve in a similar manner during previous hospitalizations when Cortisone had not been employed.

excretion of 17-ketosteroids was diminished, abnormal urinary excretions of corticosteroids were noted and adrenal reserve function was impaired.

Cortisone therapy is being used in a further series of patients in order to determine whether or not any one or combination of the above three differences is of any significance in the selection of cases in which improvement might be expected from such therapy.

Conclusions. 1) A trial of Cortisone therapy would appear to be worth while in certain cases of regional enteritis or ulcerative colitis, particularly in critically ill patients when the situation is desperate and a temporary period of improvement is desired in order to permit sufficient time for the effective use of other therapeutic measures.

2) The use of the compound does not promise to cure the disease, as a relapse may well occur following cessation of its administration.

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MYOCARDIAL INFARCTION: A STUDY OF THE ACUTE PHASE IN 920 PATIENTS*

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Coronary artery disease has increased in the past 30 years until it is now the most common type of heart ailment. This is especially true of coronary artery thrombosis with myocardial infarction. This is due partly to factors which have decreased death rates of infectious diseases, allowing a greater percentage of the population to reach age groups commonly afflicted with atherosclerotic circulatory diseases. Improved diagnostic facilities and a clinical awareness of the problem have also, to some extent, been responsible for this increase.

We are presenting 920 cases of acute myocardial infarction from the records of the Henry Ford Hospital, covering the period from 1925 to May 1, 1949. The cases were selected from 2,024 cases indexed during this period as coronary thrombosis with myocardial infarction. Cases were selected to fulfill the criteria of follow-up for 6 weeks from onset of the condition. Only cases were used which were objectively diagnosed from either 1) clinical course and electrocardiographic study or 2) demonstration at autopsy of recent myocardial infarction.

Many reports[2,3,4,6,7,11,14] have been made regarding the various diagnostic and prognostic aspects of this disease. However, we shall present only the statistics which have been gathered from this study. The cases occurred in the general population of a busy industrial city, where many people live under stress of production-line working conditions and the pressure of working to meet deadlines is felt by all. These figures could be different from those in rural districts. Also, several nationalities were represented.

The utilization of various clinical data, such as leukocyte counts, sedimentation rates, blood pressure changes, and the mental status of the patient, as prognostic signs, have been stressed in the literature. Because many of our patients were seen first on different days from the onset of symptoms (from the 1st day to 2 weeks), we found it difficult to correlate some of these features with the eventual outcome of the case. However, many factors were elicited by history and physical examination which we wish to discuss either as playing a contributing role in the cause of the attack or as a contributing influence on the eventual outcome. Complications arose dur-

*Read before the American Clinical and Climatological Society, October 18, 1950.

ing the course of illness which we shall consider as to their influence on the individual case. We shall also discuss the management of these complications.

Analysis of Cases. Table 1 lists the total number of cases according to sex, location of the infarction, and whether the patient received anticoagulants. Among these 920 cases there were 214 deaths, an overall mortality rate of 23.2%.

AGE AND SEX DISTRIBUTION. This series comprises 749 males and 171 females, a ratio of 4.4 males to 1 female. In the series of Billings *et al.*[2], from Nashville, the ratio of males was 2.7 to 1 female. Chambers[3] in New York and Mullins[8] in Pittsburgh had ratios of 3 males to 1 female. Mintz and Katz[7] in Chicago, gave a figure of 2.2 males to 1 female, and Parkinson and Bedford[10] had 13 males to 1 female. The mortality rate for the females was somewhat higher than that for the males. On an average, the females were older than the males at the time of death. There were 61% of the females and 49% of the males beyond age 60. Other authors found essentially this same sex difference. In the Mintz and Katz[7] series the average age of the females at the time of death was 63.4 years, and of the males 59.6.

Tabulation of the patient's age at the onset revealed that women were somewhat older at the time of their initial attack. In most males, the initial attack occurred in the 6th decade, whereas in females the onset was not until the 7th decade. Other series[2,3,6,7,8] have shown that the females were on an average from 3 to 6 years older than the males at the time of the onset of their illness. There were only 2 women below age 40, both of whom survived their attack. There were 34 men less than 40 years of age; 2 men were less than 30, one being 24. The mortality rates in the various decades of life are shown in Chart 1, together with the relative incidence and mortality in both sexes. Both sexes show similar mortality rates after the 6th decade. The mortality rate in the females in the 6th decade was strikingly higher than that in the males. The number of attacks occurring in the males was greater.

SEASONAL INCIDENCE. In Chart 2 the monthly incidence and number of deaths are shown. No definitely significant peaks appear except in November and then the increase was only slightly above the average. There is a fairly even distribution throughout the year. The greatest mortality peaks occurred in March and November and

TABLE 1.—MORTALITY AS RELATED TO SEX AND LOCATION OF INFARCTION. COMPARISON OF PATIENTS RECEIVING ANTICOAGULANTS WITH THOSE RECEIVING NO ANTICOAGULANTS

Sex	*Location of infarction*	*Received no anticoagulants*		*Received anticoagulants*	
		Total	*Deaths*	*Total*	*Deaths*
Male 749 cases	Anterior	353	92 (26.0%)	88	10 (11.3%)
	Posterior	234	46 (19.6%)	60	7 (11.6%)
	Unknown	11	6 (54.5%)	3	1 (33.3%)
	TOTAL	598	144 (24.0%)	151	18 (11.9%)
Female 171 cases	Anterior	74	30 (40.5%)	23	6 (26.0%)
	Posterior	56	10 (17.8%)	15	3 (20.0%)
	Unknown	3	3 (100%)	0	0 (0.0%)
TOTAL Both sexes		133	43 (32.3%)	38	9 (23.6%)
		731	187 (25.4%)	189	27 (14.2%)

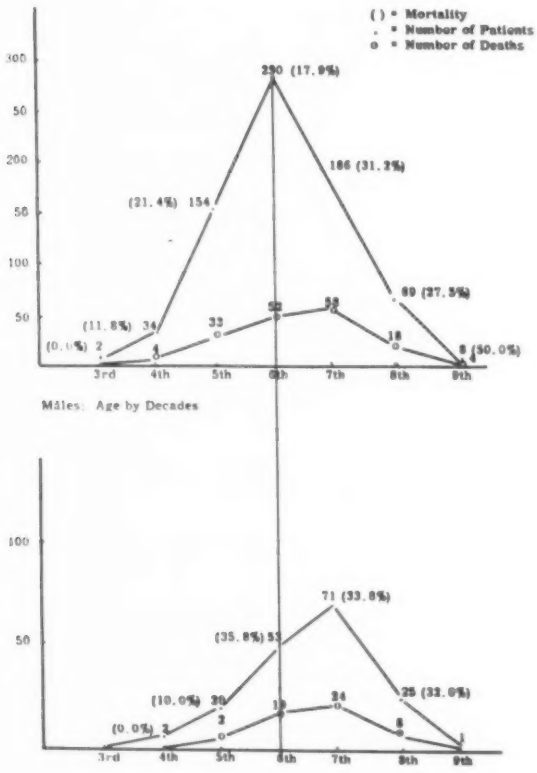

CHART 1.—FEMALES: AGE BY DECADES

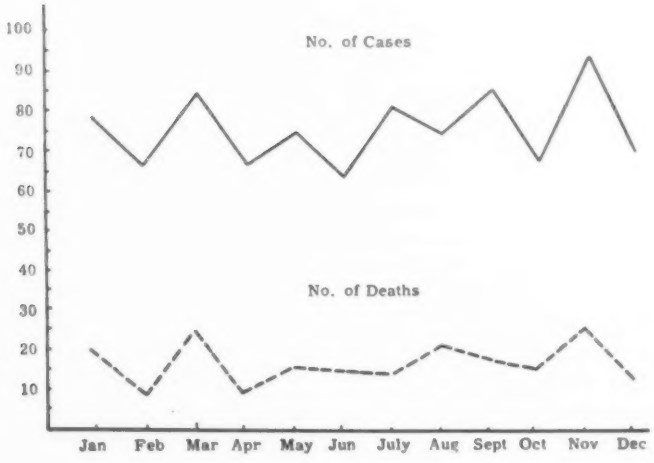

CHART 2.—MONTHLY INCIDENCE

TABLE 2.—ETIOLOGICAL FACTORS
AGE, SEX, AND MORTALITY BY DECADES

Decade of life	*3rd*	*4th*	*5th*	*6th*	*7th*	*8th*	*9th*	*Total*	
Hypertension									
36.8% Male	1	8	54	109	80	20	4	276	
Deaths	0	1	8	16	22	7	2	59	(21.3%)
67.2% Female	0	1	13	37	47	17	0	115	
Deaths	0	0	1	10	15	3	0	29	(25.2%)
Angina Pectoris									
47.7% Male	0	1	66	153	105	29	3	357	
Deaths	0	1	9	33	25	8	1	77	(21.5%)
53.8% Female	0	2	8	28	39	15	0	92	
Deaths	0	0	1	6	12	5	0	24	(26.0%)
Obesity									
28.1% Male	1	13	41	84	59	12	1	211	
Deaths	0	0	3	7	11	1	0	22	(10.4%)
32.6% Female	0	1	11	38	31	9	0	90	
Deaths	0	0	0	10	13	3	0	26	(28.8%)
Diabetes									
8.4% Male	1	2	11	28	17	4	0	63	
Deaths	0	0	1	5	6	0	0	12	(19.0%)
20.4% Female	0	0	2	13	13	7	0	35	
Deaths	0	0	0	4	3	1	0	8	(22.8%)
Previous Myocardial Infarct									
14.5% Male	0	3	21	41	34	10	0	109	
Deaths	0	1	11	11	12	1	0	36	(33.0%)
9.4% Female	0	0	1	9	6	0	0	16	
Deaths	0	0	0	1	2	0	0	3	(18.7%)
Silent									
Male	0	0	4	2	6	1	0	13	
Female	0	0	1	0	0	0	0	1	
Syphilis									
Male	0	1	3	4	5	2	0	14	
Female	0	0	0	0	0	0	0	0	

seemed to parallel the number of cases each month.

OCCUPATION. In this series 34.2% were in the laboring group, 18.0% unskilled labor, and 16.2% skilled labor. Housewives made up 21.6% of the total. Business, professional, and executive men made up 28.8% of the total; salesmen 6.6%, retired 4.8%, unemployed 2.4%, and farmers 1.2%.

FACTORS FROM THE HISTORY AND PHYSICAL EXAMINATION. In Table 2 are tabulated factors obtained from the history and physical findings of these patients.

HYPERTENSION. Hypertension existed in 36.8% of the men and 67.2% of the women. Many other authors have reported approximately the same incidence. In Mintz and Katz'[7] large series, 35.9% of the patients had hypertension. In Master's[6] somewhat smaller series 69% of the patients had hypertension. Its incidence is much greater in women than in men in most series. However, many authors have concluded that the factor of hypertension had no influence on the immediate mortality. As seen in Table 2, our statistics bear this out. The mortality rate for the males with hypertension was 21.3%, and the mortality rate for the females with hypertension was 25.2%.

ANGINA PECTORIS. Angina pectoris occurred in 47.7% of the men and 53.8% of the women. From the statistics of this series, its presence seemed to have no effect on the mortality rate. There were 357 males with angina pectoris with 77 deaths, a mortality rate of 21.5%. Ninety-two females had hypertension with 24 deaths, a mortality rate

of 26.0%. Site of the infarction in those with antecedent angina was in the same proportion as it appeared in the study as a whole. Mintz and Katz[7] found it equally common in the two sexes; 72.9% of their patients had an antecedent history of angina pectoris. The mortality rate in their series was 23.3% for men and 28.0% for women.

TABLE 3.—ANGINA PECTORIS: RELATION TO INFARCTION DURATION

Sex	*1 wk.*	*2 wks.*	*3 wks.*	*¼ wks.*	*1 to 6 mos.*	*Over 6 mos.*
Male	36	27	14	31	72	184
			TOTAL 108			
Female	6	7	2	8	15	52
			TOTAL 21			

Many of the cases in this series had the onset of pilot attacks of angina varying from a few days to a few weeks prior to the onset of their myocardial infarction. This is shown in Table 3. One hundred and eight males had angina pectoris of less than one month's duration, and 21 females had angina of less than one month's duration, a total of 129 cases for the series and an incidence of 15.1%. The mortality rate of this group, however, was no greater than the mortality rate of the group who had angina of longer standing. Because this pattern was found so frequently, many patients subsequent to this study have been hospitalized when found to be having pilot anginal attacks. They were placed on anticoagulant therapy, and a subsequent analysis of this group will be attempted to evaluate the efficacy of this treatment.

OBESITY. This factor occurred in 28.1% of the men, and 52.6% of the women. There were 211 cases of obesity in the males with 22 deaths, a mortality rate of 10.4%. It occurred 90 times in the female group with 26 deaths, or a mortality rate of 28.8%. Billings *et al.*[2] state that the immediate mortality of the obese patients in their group was 32%, for patients of average weight 39%, and for the underweight group 60%. The actual mortality rate for obese patients in this series is below the overall mortality rate for both sexes and seems in keeping with the figures just stated.

DIABETES MELLITUS. This condition was found in 8.4% of the men and 20.4% of the women in this series. No significant difference in the mortality rates of the diabetics and non-diabetics was found. There were 63 cases in the male group with 12 deaths, a mortality of 19.0%; 35 cases among the female group with 8 deaths, a mortality of 22.8%. Other authors[6,7] have concluded that diabetes mellitus added considerably to the gravity of the prognosis in women. The figures from this series do not bear this out.

PREVIOUS MYOCARDIAL INFARCTION. This condition occurred with an incidence of 14.5% in the males and 9.4% incidence in the females. There were 109 men with previous myocardial infarctions with 36 deaths, or a mortality of 33%. Sixteen females in this series had previous myocardial infarctions with 3 deaths occurring, a mortality rate of 18.7%. From these figures it would seem that a previous myocardial infarction in the male added considerably to the gravity of a new infarct.

SYPHILIS was found in only 1.8% of this series. In only 1 patient was it proved to be a definite etiological factor in his illness. This patient was a 38-year old colored man who, at autopsy, had marked narrowing of the coronary ostia secondary to luetic involvement of the aorta.

Silent myocardial infarctions are extremely rare. There were 14 cases in this series. Mintz and Katz[7] found 18 cases of silent myocardial infarction in their series of 572 cases. It did not seem to influence the mortality rate in our series.

PRECIPITATING FACTORS. Master[5] is of the school that accepts no cause except shock or shock-like states as direct precipitating factors in coronary artery occlusion. In coronary insufficiency, however, he finds that there are etiological factors. These are increased cardiac work, diminished coronary flow, and impaired oxygenation of the blood (usually occurring in combination). Either coronary occlusion or coronary insufficiency may result in acute myocardial infarction.

A history of onset occurring during the usual routine of day to day life was obtained in the majority of these cases. Possible precipitating factors occurred in 60 cases, an incidence of 6.5%. These included such activities as strenuous physical exertion, bowling, driving an automobile, following a heavy meal, emotional crises, during hospitalization, postoperatively, and after massive hemorrhage, diabetic acidosis, chest trauma, the use of pitocin, bronchograms, and venipuncture. The majority of cases in this series occurred during ordinary routine daytime activity or while at rest, either awake or during sleep.

Several disease states were found coincident with the attack, as follows: 8 cases of cerebral vascular accident, 11 of gall bladder disease, 6 of peptic ulcer, 6 of uremia, 3 of gout, 3 of pneumonia, 3 of pulmonary emphysema, 2 of myxedema, 2 of hyperthyroidism, 5 of carcinoma, 1 of acute fibrinous pericarditis following pneumonia, 2 of polycythemia vera, and 1 of pernicious anemia. Rheumatic heart disease was found in 8 cases, and a history of preexisting congestive heart failure was obtained in 28 cases.

LEUKOCYTE COUNT. The mortality rate seemed to rise in proportion to the leukocyte count, in accordance with reports by other observers[2,3,11]. This is given in Chart 3; the mortality rate was 11% when the count was 10,000 and below, 13% when it was 10,000 to 15,000, 28% when it was 15,000 to 20,000 and 38% when it was over 20,000.

SITE OF INFARCTION. The majority of the myocardial infarctions in this series occurred in the anterior wall of the left

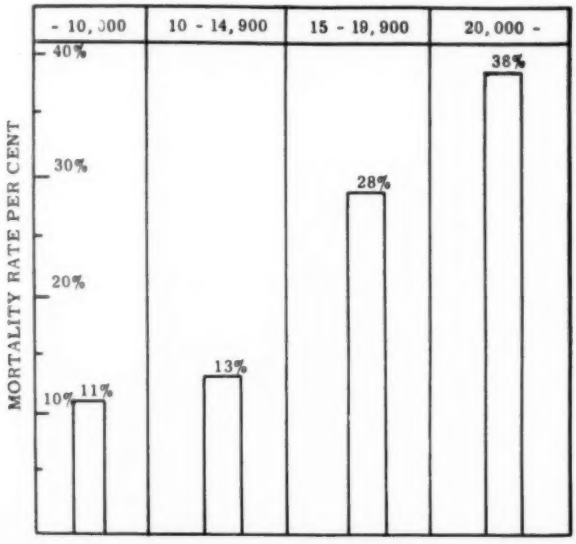

CHART 3.—LEUKOCYTE COUNT

ventricle. There were 538 anterior infarctions with mortality 27.7% and 365 posterior infarctions with an 18.1% mortality.

Table 1 breaks this down further as to the influence of sex and whether anticoagulants were received. There were 353 males with anterior myocardial infarctions with 92 deaths. The mortality rate was 26% in the group which did not receive anticoagulants, as compared to 74 cases of anterior infarction in the female with 30 deaths, a mortality rate of 40.5%.

Posterior myocardial infarction occurred 234 times in the male group that did not receive anticoagulants with 46 deaths, a mortality rate of 19.6%, and 56 times in the female group with 10 deaths, or a 17.8% mortality rate.

In the group receiving anticoagulants and with anterior myocardial infarction there were 88 males with 10 deaths, a mortality rate of 11.3%, and 23 females with 6 deaths, a mortality rate of 26%. Posterior myocardial infarction occurred in this group in 60 males, with 7 deaths, a mortality rate of 11.6%; and

TABLE 4.—BREAKDOWN OF THROMBOEMBOLIC COMPLICATIONS

Days		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*3rd wk.*	*4th wk.*	*5th wk.*	*6th wk.*	*Total*
Pulmonary infarction	M		3	5	3	5	3	3	4	4	2	2	3	1	2	13	4	4	4	
	F			2	3	2	2	1	1		1		1			3	1	2		
Total days			3	7	6	7	5	4	5	4	3	2	4	1	2					
Total wks.								32							21	16	5	6	4	84
Cerebral embolus	M		1	1		1		3	1	1		1		1		2	1		2	
	F			1		1						1				1				19
Phlebitis	M													1			1		1	
	F	1											1							5
Mesenteric embolus	M		1	1												1				
	F																			3
Emboli to extremities	Popliteal			1						1			1	1			1	1		
	Femoral		1									1				2				
	Brachial						1													
	Iliac saddle									1							1			13
Splenic infarct			1	2	1				1						1	1			1	8
Renal infarct			1													2	1	1	1	6
Extensions	M			1	2	2				1	4	3			2	4	5	1	1	
Primary	F				1												2			29
New area	M				1							1	1	1	1					
	F															1		1		7
TOTAL		1	8	14	11	11	6	7	7	8	7	9	7	5	6	30	17	10	10	174
								58 1st wk.							49	2nd wk.				

TABLE 5.—THROMBOEMBOLIC COMPLICATIONS

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*After 10 days*
No anticoagulants											
142 patients		7	9	7	10	8	6	7	3	5	105
166 embolic episodes											
Dicumarol											
120 patients									1		2
Dicumarol & Heparin											
87 patients									1		3

in 15 women, with 3 deaths, or a 20% mortality rate.

The mortality rate differs with the site of the infarction. It was higher in the group of anterior infarcts occurring in females. There was little sex difference in the posterior group with or without anticoagulants. Various complications of acute myocardial infarction will be discussed under a separate heading revealing their relationship to the site of the infarct.

Other series indicating anterior infarction to be more serious are those of Vander Veer and Brown[14], Stroud[13], and Wood *et al.*[17]. No significant difference in mortality in anterior and posterior infarctions was reported by Billings[2], Master *et al.*[6], Willius[16], Barnes and Ball[1], and Levine and Brown[4]. From statistics alone the series of Mintz and Katz[7] suggests that posterior infarction has a more serious outlook.

THROMBOEMBOLIC COMPLICATIONS. Table 4 shows the thromboembolic complications according to the day and the week of illness. This is broken down into the different sexes and site of occurrence. The occurrence of 58 in the 1st week and 49 in the 2nd week are the peak numbers. This is 34.9% of the total for the 1st week and 29.5% for the 2nd week. The numbers rapidly diminish after this period. The large numbers which occurred during the 1st week of illness, especially the first 3 and 4 days, would indicate the rationale of starting anticoagulants promptly to combat the early occurrence of these conditions.

However, in our series a comparison of cases of myocardial infarction receiving dicumarol alone with those given heparin initially as well did not reveal any advantage for the latter group in the avoidance of thromboembolic complications (Table 5). The fact that no such complication occurred in the first week among 142 cases treated with dicumarol alone, despite the well known lag of 48 to 72 hours in arriving at a prothrombin time of 30 to 35 seconds, suggests that, despite this lag, dicumarol probably has an appreciable immediate anticoagulant effect prior to the development of the prothrombin level usually regarded as effective, that is, 30 to 35 seconds.

The breakdown as to site of thromboembolic complications indicates, as has been the case in most series, that the majority of these lesions are pulmonary infarctions; 32 cases of pulmonary infarction occurred in the 1st week, 21 the 2nd week, and 16 the 3rd week, with a rapidly diminishing number in the 4th, 5th and 6th weeks. When symptoms and signs of coronary occlusion recurred without evidence of electrocardiographic changes in a new area, the cases were classified as an extension of the primary infarction. When new electrocardiographic changes occurred, they were classified as extensions in a new area.

TABLE 6.—THROMBOEMBOLIC COMPLICATIONS: MORTALITY

Sex	*No. cases*	*No. deaths*	*Mortality*
Male	114	48	42.17%
Female	28	12	42.9%
TOTAL	142	60	42.2%

* Of a total of 731 cases receiving no anticoagulants, 142 patients had thromboembolic complications (19.4% incidence). These 142 patients had a total of 166 thromboembolic episodes.

In Table 6 are tabulated the mortality rates associated with thromboembolic complications as to sex. In this group a total of 731 patients received no anticoagulants. Of these, 142 patients had thromboembolic complications, an incidence of 19.4%. There was a total of 174 thromboembolic episodes. In that group of patients having thromboembolic complications, the mortality rate was 42.2% as compared to a mortality rate of 19.8% in the group that did not have thromboemboli.

There were 189 cases that received anticoagulants. Fifteen of these patients had thromboembolic episodes, an incidence of 7.9%, as compared to the 19.4% incidence in the group that did not receive anticoagulants. In the group that received anticoagulants, there were 8 cases that had a thromboembolic episode before anticoagulants were started. These are not included in the total number of thromboembolic complications. However, in 7 thromboemboli occurred after the anticoagulant was stopped, and these are included.

In the group receiving anticoagulants (Table 1), there was a total of 151 cases in the males with 18 deaths, a mortality rate of 11.9%. There was a total of 38 cases with 9 deaths, an over-all mortality rate of 23.6%, in the females that received anticoagulants; a total of 189 cases in both sexes with 27 deaths, an over-all mortality rate of 14.2%, for the group receiving anticoagulants.

The incidence of thromboemboli in the series of Mintz and Katz[7] was 9.9%. This group had a mortality rate of 55.8%. Nay and Barnes[9] encountered thromboemboli in 37 of 100 consecutive patients.

ARRHYTHMIAS. An arrhythmia occurred in some form in 16.3% of the total group.

Extrasystoles were encountered more frequently than any other arrhythmia. However, we doubt that the figures presented here represent the true incidence of this arrhythmia. It probably occurs much more frequently than the figures indicate. However, in the patients with extrasystoles the mortality rate was higher than for the group as a whole. Table 7 shows the incidence and the number of deaths broken down for nodal, auricular, and ventricular extrasystoles.

In the 63 cases in which ventricular extrasystoles occurred, there were 23 deaths, a mortality rate of 36.5%. There was 1 death in the 7 cases having auricular extrasystoles. Nodal extrasystoles were recorded in 1 case.

TABLE 7.—PREMATURE BEATS

Type	*Total No. cases*	*Total No. deaths*	*Mortality*
Nodal	1	0	0
Auricular	7	1	14.3%
Ventricular	63	23	36.5%
No quinidine	26	10	38.4%
Quinidine	37	13	35.1%
TOTAL	71	24	33.8%

Incidence 7.7%

There were 26 patients having ventricular extrasystoles that did not receive quinidine. Ten deaths occurred, a mortality rate of 38.4%.

There were 37 cases of ventricular extrasystoles that received quinidine. There were 13 deaths in this group, a mortality rate of 35.1%. This does not represent any favorable change in mortality in the group receiving quinidine.

There was a total of 71 cases in the whole series in which premature beats were recorded, an incidence of 7.7% with 24 deaths, or a mortality rate of 33.8%. This suggests that the occurrence of extrasystoles has importance as far as the mortality rate is concerned. The frequency of their occurrence needs much closer checking, and the use of quinidine as a prophylactic measure following the appearance of premature beats needs further evaluation.

The appearance of an arrhythmia other than premature beats is generally regarded to be more serious than premature beats, and in this series did affect the mortality rate appreciably. The males having these arrhythmias had an over-all mortality rate of 30.3%. The females had a mortality rate of 53.8%. These figures are recorded in Table 8. In such patients encountered by Mintz and Katz[7], the mortality rate

TABLE 8.—ARRHYTHMIA

Sex	*Type of Arrhythmia*	*No. cases*	*No. deaths*	*Mortality*
Male	Auricular fibrillation	34	9	26.5%
	Ventricular Tachycardia	12	7	58.3%
	Complete Heart Block	10	5	50.0%
	Nodal Tachycardia	3	1	33.3%
	Auricular Flutter	4	0	0.0%
	Auricular Tachycardia	3	0	0.0%
Female	Auricular Fibrillation	10	5	50.0%
	Ventricular Tachycardia	1	1	100.0%
	Complete Heart Block	1	1	100.0%
	Nodal Tachycardia	1	0	0.0%

TABLE 9.—AURICULAR FIBRILLATION: CONVERSION AND MORTALITY

		Anterior	*Posterior*	*Unknown*
Total		20	20	4
Deaths		4	8	2
Conversion	Spontaneous	4	8	1
	Digitalis	4	4	2
	Quinidine	2	2	0
	Quinidine & Digitalis	3	0	0
Failed to convert (received Digitalis)		6	4	1
Failed to convert (no Digitalis)		1	2	0

TABLE 10.—AURICULAR FIBRILLATION: PERIOD OF ONSET

Day	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*2nd wk.*	*3rd wk.*	*4th wk.*	*5th wk.*	*6th wk.*
No.	13	3	7	4	4	2	5	4	0	1	1	0
						TOTAL 1ST WK.	38	4	0	1	1	0

TABLE 11.—VENTRICULAR TACHYCARDIA: 13 PATIENTS

Type	*Deaths*	*Recovered*	*Total*	*Day of onset*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*14*	*15*	*16*	*17*	*18*
Anterior	6	3	9	TOTAL	5	3	1	0	2	0	0	0	1	0	0	1
Posterior	1	2	3													
Unknown	1	0	1													

was 43.6% for the group and 66.7% for the females of that group.

Auricular fibrillation was seen more often than the other arrhythmias. This arrhythmia occurred 44 times in this series and is covered in Table 9, which shows the effects of the various combinations of digitalis and quinidine used in the therapy of this arrhythmia.

There were 20 cases each in the anterior and posterior groups. Four cases occurred in the unknown group. The incidence appears to be greater in the posterior group as there was a smaller number of this type of infarction. Fourteen deaths occurred, a mortality rate of 31.8%. Of 16 cases receiving neither digitalis or quinidine, 13 converted to sinus rhythm spontaneously. Twenty-eight cases received digitalis or quinidine, or a combination of the two, in an effort to effect con-

version to sinus rhythm. Ten cases converted with digitalis alone, 4 with quinidine alone, and 3 with quinidine and digitalis. Eleven cases received digitalis and failed to convert. Digitalis alone was not given for the purpose of converting the arrhythmia to normal, but to control the rate or because the patient was in congestive heart failure. The majority of the cases having auricular fibrillation occurred during the first week of illness (Table 10).

Ventricular tachycardia was demonstrated by electrocardiograph on 13 occasions. It occurred most often during the first 5 days of illness. Both of the 2 patients in whom the arrhythmia occurred on the 15th and 18th days from onset had received digitalis shortly before the arrhythmia appeared.

The high mortality rate associated with ventricular tachycardia is evident from Table 11. In only 1 instance was spontaneous conversion to sinus rhythm recorded. In more recent cases we have been more vigorous in our therapy with quinidine both orally and parenterally, and seemingly have been more successful in stopping these attacks. Table 11 shows the extremely high mortality rate associated with this arrhythmia, there being 9 cases of anterior myocardial infarction with 6 deaths and 3 posterior myocardial infarctions with 1 death. It occurred once in an unknown type with death occurring in this case. An over-all mortality rate of 61.5% is recorded in patients with this arrhythmia.

Congestive Heart Failure. This condition occurred in 156 of the cases of this series, an incidence of 16.9%. The appearance of congestive heart failure following acute myocardial infarction is ominous. The mortality rate for the complication was about the same for both sexes: 56.9% for the males and 57.7% for the females (Table 12). Of the 156 patients with this complication, 67% of them, 105 cases, occurred during the first week of illness, and in these the mortality rate was particularly high although many did not die until the second week of illness (Table 13).

TABLE 12.—MORTALITY, CONGESTIVE FAILURE

Sex	*Total*	*Deaths*	*Mortality*
Male	130	74	56.9
Female	26	15	57.7

Digitalis was used in the patients most seriously ill of congestive failure. Many of those who were in failure of mild degree were treated by restricting the sodium intake and giving ammonium chloride and mercurial diuretics. However, in the group that did receive digitalis (these patients undoubtedly were more seriously ill), it seemed to influence the outcome favorably when compared with those having no digitalis (Table 14).

There was a total of 57 cases that did not receive digitalis with 37 deaths, a 64.9% mortality rate; and in 99 cases that did receive digitalis there were 53 deaths, a 53.5% mortality rate. Of the 538 cases of anterior myocardial infarctions, congestive failure occurred in 98, an incidence of 18.2%. Of the 365 cases of posterior myocardial infarction, 47 had congestive failure, an incidence of 12.8%. There were 17 unknown types of myocardial infarction with congestive failure occurring in 11, a 64.7% incidence. The high incidence of congestive failure occurring in this group is explained by the fact that many who had unknown sites of infarction had a left bundle branch block, which would indicate a serious conduction defect and the existence of rather extensive heart disease.

Ventricular Rupture. Ventricular rupture was encountered in 8 cases. The day of occurrence of the rupture and the presence or absence of angina pectoris preceding it are tabulated in

Table 15. One patient had a history of previous infarction 1 year prior to his terminal illness. In no other instance was there a history of angina pectoris of longer than 4 weeks' duration. Wessler, Schlesinger, and Zoll[15] have emphasized that individuals having myocardial rupture are relatively free of antecedent coronary disease and unprepared for injury. They also observed that these patients had a significantly higher incidence of 1) sustained hypertension during infarction and 2) unusual effort during the last 24 hours of life.

Discussion. This study concerns a large number of patients with acute myocardial infarction as observed in the dynamic city of Detroit, and it may offer some points of interest to be compared with similar experiences in other centers.

The data presented indicate a fairly even distribution of cases throughout the months of the year, and slightly increased number in November (95 as compared to 86 in September, the next highest month).

In this series the cases were somewhat more preponderantly male than in several previously reported series.

The peak incidence in men occurred in the 6th decade, while in women it was in the 7th (Chart 1). Several

TABLE 13.—CONGESTIVE FAILURE. 156 PATIENTS: PERIOD OF ONSET

Day	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*1st wk.*	*2nd*	*3rd*	*4th*	*5th*	*6th*	*Unknown*
Anterior	30	6	6	4	10	6	4		14	9	1	1	0	8
Posterior	8	5	5	4	3	4	2		9	1	2	1	1	1
Unknown	5	0	0	1	0	1	1		0	2	1	0	0	0
TOTAL	43	11	11	9	13	11	7	105	23	12	4	2	1	9
Death*	10	13	8	6	10	11	3	61	20	5	3	0	0	0

* Day of death regardless of time of onset

TABLE 14.—CONGESTIVE FAILURE

	No digitalis		*Digitalis*		*Total with failure*	*Total No. of cases*	*% with congestive failure*
	Total	*Deaths*	*Total*	*Deaths*			
Anterior	38	23 (60.5%)	60	30 (50.0%)	98	538	18.2%
Posterior	14	10 (71.4%)	33	19 (57.5%)	47	365	12.8%
Unknown	5	4 (80.0%)	6	4 (66.6%)	11	17	64.7%
TOTAL	57	37 (64.9%)	99	53 (53.5%)	156	920	16.9%

TABLE 15.—VENTRICULAR RUPTURE

No.	*Age*	*Sex*	*Date of rupture*	*Type infarct*	*Previous angina other remarks*
1	73	Male	? "Silent"	Anterior	No previous angina
2	47	Male	12th day	Anterior	No previous angina
3	56	Male	6th day	Anterior	Previous infarct 1 year before
4	59	Male	6th day	Posterior	Angina 4 weeks, hypertension, obesity
5	53	Female	6th day	Anterior (apex)	Angina 2 weeks, hypertension, obesity
6	38	Male	26th day	Anterior	Angina 2 weeks, mural thrombi
7	60	Female	23rd day	Anterior (apex)	Obesity, mural thrombi
8	66	Female	12th day	Anterior	Hypertension, obesity

cases occurred in men in the 4th decade, but in women only 2 before the 5th. At the peak incidence of the disease, female mortality rate was higher than male, 33% compared to 17.9%, though at 70 and beyond the mortality rate curve is the same in both sexes (Chart 1). The mortality rate in the females in the 6th decade was strikingly higher than that in males in the 6th decade.

Hypertension appeared to have no bearing on immediate mortality and obesity did not increase the immediate hazard.

Preceding angina pectoris was present in about one-half the cases but had no effect on the mortality rate. However, since 15% of this group had pilot angina of less than 1 month's duration, it has been our recent custom to hospitalize for 2 weeks those patients showing such symptoms and to administer prophylatic anticoagulants. Our impression is that this has been beneficial in both the relief of the frequent angina and in the prevention of imminent myocardial infarction. It is difficult to escape the impression that dicumarol has a distinct coronary dilator action, since the relief of anginal distress in many cases has been so striking with this agent.

This review suggests that in men a history of a previous myocardial infarction adds considerably to the immediate hazard of a new infarction. An insufficient number of women having such history was studied to permit definite conclusions regarding them.

While the incidence of diabetes seemed to increase the tendency to myocardial infarction in women, the prognosis in this group for immediate mortality was not greater than in the non-diabetic female.

The benefits of anticoagulants in decreasing the incidence of thromboembolic episodes and lowering mortality was evident and was much the same as in other series[18]. Because of the significant number of early thromboembolic episodes encountered, there seemed to be confirmatory evidence that the immediate initial use of heparin was justified to overcome the lag in the dicumarol effect; but a comparison of cases in which heparin was added initially with another series in which dicumarol alone was used, showed that no advantage seemed to be gained by the use of heparin over treatment with dicumarol alone. Avoidance of the use of a parenteral anticoagulant spares the patient both annoyance at a time when rest is of paramount importance, and also considerable expense later.

The most vulnerable individual, from the mortality standpoint, seems to be the female with anterior infarction. In general, the immediate prognosis for anterior infarction is more serious than for posterior, but our previous report[12] indicated that the over-all mortality after the elapse of 5 or more years shows the outcome to be the same.

Paroxysmal ventricular tachycardia was an extremely ominous development. The difficulty of handling it with ordinary doses of quinidine has led us recently to use considerably larger doses. We control the administration of the drug by frequent direct-writer electrocardiograms. Intravenous quinidine (quinidine lactate) has been successful in several instances where oral quinidine could not be used or was unsuccessful.

The use of prophylactic quinidine in patients showing premature beats deserves further evaluation, since a comparison of mortality rates in such patients who received the drug with an equal number who did not shows no decided advantage for either group.

The indication or contraindication for digitalis in cardiac failure complicating myocardial infarction has long been one about which there was no general agreement. A study of these

figures would indicate that these patients have a somewhat better chance of survival if they are digitalized than if they are not. Therefore, the use of digitalis in patients with myocardial infarction who show evidence of congestive cardiac failure is recommended.

The fact that all but one of the cases of ventricular rupture occurred in individuals who had had no history of previous coronary occlusion or of long standing angina does suggest that these patients were less able to survive the shock of sudden interruption of a portion of the coronary artery circulation without more extensive and serious muscle damage than those in whom previous coronary narrowing or occlusion may have led to the development of an increase in the anastomotic circulation of the coronary system.

Summary. 1. A review of the clinical records of 920 cases of acute myocardial infarction has been presented.

2. The mortality rate was found to be influenced significantly by the sex of the patient, the age at onset, the site of the myocardial infarction, the degree of leukocytosis; the presence of thromboembolic complications, of cardiac arrhythmias, and of congestive heart failure, and the history of a previous myocardial infarction.

3. No influence on the mortality rate was found when hypertension, angina pectoris, diabetes mellitus, and obesity were present, although they were encountered frequently in this group.

4. The various therapeutic measures attempted were tabulated. Anticoagulant therapy had the most distinctly favorable influence on the mortality rate. Dicumarol alone seemed as effective as dicumarol plus initial heparin in preventing thromboembolic episodes. Digitalis seemed beneficial in treating congestive heart failure; certainly no distinctly unfavorable effect was evident. Quinidine in adequate doses influenced favorably the outcome of a few cases of ventricular tachycardia. Neither digitalis nor quinidine appeared to be particularly beneficial in the conversion of auricular fibrillation to sinus rhythm.

5. The incidence of ventricular rupture and the contributing factors preceding its appearance are discussed.

6. The high incidence of premonitory pain occurring for a few days to four weeks prior to acute myocardial infarction was striking in this series.

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BRONCHIECTASIS: A STUDY OF 220 PROVED CASES

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IN 1947 bronchiectasis was referred to as "a neglected disease" by two separate authors[5,12]. A number of other investigators prior to and since this date have indicated that they are of a similar opinion. This negligence related to bronchiectatic disease would seem to be essentially two-fold: 1) the diagnosis is not made sufficiently early, and 2) once the diagnosis has been established, surgical treatment is too infrequently suggested. It was for the purpose of obtaining data pertinent to these two problems that 220 cases of proved bronchiectasis were reviewed with special attention accorded to the incidence and character of the clinical features of this disorder which might have bearing on earlier diagnosis, and to the reason (or reasons) why surgical therapy was not utilized in the medically treated patients.

The chapter on bronchiectasis in Graham, Singer, and Ballon's text[3] and Lisa and Rosenblatt's contribution[8] on this same subject very adequately cover the pathological, clinical, and therapeutic aspects of the disease up to 1943. Data obtained from these two sources relative to the characteristics of bronchiectasis and analysis of like material from articles in the more recent literature reveal little unanimity of opinion concerning the incidence, importance, or significance of its various morbid features. There are a few exceptions, however. There is a consensus that bronchiectasis is a relatively common pulmonary disease; that bronchopneumonia is the most frequent precursor of bronchiectasis; that bronchiectasis most commonly has its onset in early life; and that it is equally distributed between the sexes.

Some examples of the divergent and conflicting statements which may be found in the literature are these: "few with proven bronchiectasis live beyond the age of forty"[12], as compared with 23% of one series[3] and 34% of another[9] where the patients were 40 years of age or more when a diagnosis of bronchiectasis was made. Hemoptysis was present in 10% of the cases of one series[6], in 50% in another[14], and in 80% of a third[1]. Clubbing of the digits was found in 1% of cases by Levitt[7] as compared with 57% in the series reported by Ogilvie[10]. Fetor oris occurred in 5% of one series[5] and in 33% in another[4]. Sputum production has been estimated to average 1 to 2 ounces per day[14] but has also been described as "very variable"[3] and "very profuse"[8]. Sinusitis was found in 1.3% of Laird's series[6] as compared with 79% of Farrell's[2] and 82% of Raia's[11].

If the disparity and confusion regarding the important historical features, symptoms, and signs of this disease could be resolved, the practitioner's index of suspicion as to the presence of bronchiectasis might be increased and more prompt action taken to substantiate the diagnosis by means of bronchography.

Although specialists in chest diseases are in general agreement that medical therapy for bronchiectasis is only palliative and surgical excision provides

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the sole means of "cure"[15], there remains some uncertainty as to why more patients with proved bronchiectasis are not treated by operation. Some maintain that the cases are too far advanced by the time the diagnosis is made and consideration given to surgery[13]. Others blame the family physician or the patients for refusal to accept surgical therapy[5]. To our knowledge, this matter has not previously been subjected to specific investigation in a large series of patients.

Material. The material comprising this report was derived from a review of the 285 patients with a primary diagnosis of bronchiectasis hospitalized at the State of Wisconsin General Hospital during the 10-year period from January, 1938, through December, 1947. Sixty-five cases were excluded. Thirty-nine of these were discarded because bronchography was not performed. Nineteen patients were excluded because they had active tuberculosis. In 2 cases the histories were inadequate. Three patients had bronchial tumors. Two cases were eliminated because the presence of bronchiectatic disease could not be demonstrated on examination of the specimens after surgical removal. In these 2 instances pre-operative bronchography had shown the presence of bronchial occlusion. At the time of operation both cases had a presumptive diagnosis of bronchiectasis.

It was from the remaining 220 patients with nontuberculous and proved bronchiectasis that the following data were obtained.

Results. AGE. The age in each instance was that recorded at the time of admission. Fig. 1 shows the total number of patients falling into each decade as well as the number having operation in each age group. The age distribution was remarkably symmetrical. It is noteworthy that 50% of the cases were 40 years of age or older.

SEX. Table 1 reveals that the sex distribution was essentially equal in this series. Fifty-five per cent of the patients were males and 45%, females.

ETIOLOGY. The history of each patient was studied for his idea as to the "cause" of his disease. The limitations of this approach are recognized, yet it was felt that the relative importance of some of the suspected etiological

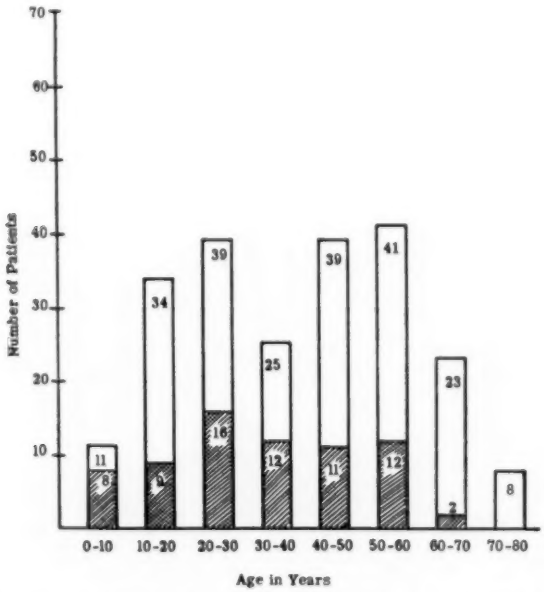

FIG. 1.—Age distribution by decades in 220 cases of bronchiectasis. Shaded portion represents number of cases treated by surgery.

factors could be elicited and compared in this manner. As shown in Table 2, 127 (58%) of the patients had no knowledge of any antecedent illness or other circumstance which they believed responsible for their bronchiectasis. The onset of the illness in these patients was insidious. Sixty-six (30%) of the patients felt that their disease resulted from "pneumonia". These patients believed themselves to be in "good health" until they had an acute pneumonic episode, following which there were persistent and progressive respiratory symptoms up to the time of admission. Eleven patients believed that "influenza" was the cause of their bronchiectasis, while 12 blamed "whooping cough". In 4 cases the presence of a foreign body was demonstrated postoperatively.

TABLE 1.—SEX DISTRIBUTION OF 220 CASES OF BRONCHIECTASIS

	Males	*Females*
Surgery	34	36
No surgery	88	62
TOTAL	122	98

TABLE 2.—ETIOLOGICAL DISTRIBUTION IN 220 CASES OF BRONCHIECTASIS

Etiology	*No. of patients*
Not known	127
Post pneumonic	66
Post influenzal	11
Post whooping cough	12
Foreign body	4
TOTAL	220

DURATION. Cough was present, to some degree, in every one of the 220 patients. Thus, an attempt to determine the duration of the bronchiectasis

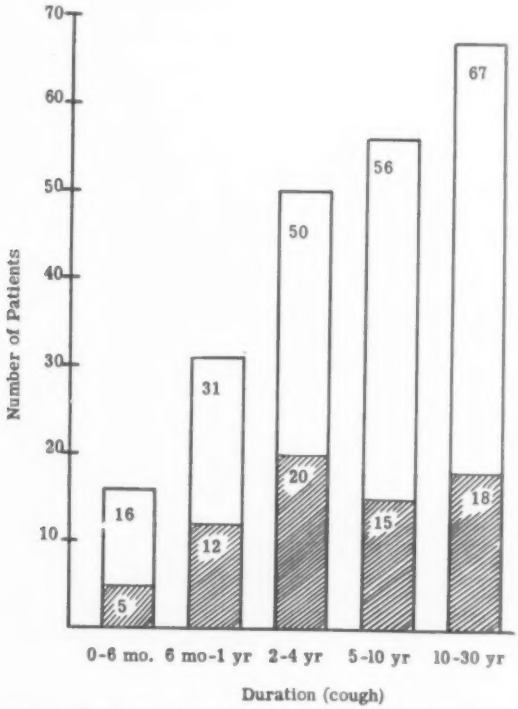

FIG. 2.—Duration (as based on presence of cough) in 220 cases of bronchiectasis. Shaded portion represents number of cases treated by surgery.

was made by computing the duration of the cough from the time of onset to the time of admission. Fig. 2 shows a step-like progression with the number of patients increasing as the duration of the illness increases. Thirty percent of the patients had coughed for 10 years or more, while 56% had coughed for over 5 years.

Amount of Sputum. The sputum production in each case was that amount produced at the time of admission as estimated by each patient. In 96 cases (43%) the amount of sputum was merely described as "productive". A quantitative estimation was made in each of the remaining cases. Fifty-seven patients (26%) produced ½ cup (60 cc.) daily. Thirty-seven patients (17%) produced 1 cup. Only 17 patients (7%) raised as little as 1 ounce, and only 13 (6%) produced as much as 2 cups of sputum daily.

TABLE 3.—PREVIOUS (OR CO-EXISTING) ILLNESSES IN 220 CASES OF BRONCHIECTASIS

Illness	*No. of patients*
"Usual Childhood Diseases"	196
Measles	24
Influenza	58
Pneumonia	**143**
Upper respiratory infections	**80**
Sinusitis	86
Allergic manifestations	71
Sinusitis and allergy	28
Sinusitis alone	58
Allergy alone	43

Previous (or Co-Existing) Illnesses. As shown in Table 3, 196 patients had "all the usual childhood diseases". The remaining 24 had measles but denied the other common childhood illnesses. Fifty-eight patients (26%) had "influenza" some time prior to admission. One hundred and forty-three patients (65%) had had "pneumonia" one or more times in the past. Although not indicated in Table 3, the majority of this latter group had repeated attacks of pneumonia, having had such a diagnosis made 2 to 4 or more times prior to admission. Eighty patients (36%) had a history of repeated upper respiratory infections. Eighty-six patients (39%) giving a history suggestive of sinusitis were proved to have this by means of sinus roentgenograms or detailed examination. Seventy-one patients (32%) gave a history of allergic manifestations including one or a combination of the following: asthma, hay fever, urticaria, eczema, nasal polyps. Comparison of the number of patients having both sinusitis and allergy with those having these conditions alone revealed that 28 patients (13%) had both, 58 patients (26%) had sinusitis alone, and 43 patients (20%) had allergic disorders without sinusitis.

TABLE 4.—INCIDENCE OF SIGNS IN 220 CASES OF BRONCHIECTASIS

Signs	*No. of patients*
Hemoptysis	**137**
Clubbing of digits	90
Fetor oris	67
Amyloidosis	0

Signs. As may be seen in Table 4, 137 patients (62%) had hemoptysis. This ranged from intermittent blood-streaking to gross pulmonary hemorrhage. Ninety patients (41%) had clubbing of the digits. Sixty-seven patients (30%) had fetor oris. Amyloid disease was suspected in several patients but was not confirmed in any case.

TABLE 5.—MODE OF CONFIRMATION OF DIAGNOSIS IN 220 CASES OF BRONCHIECTASIS

Method	*No. of patients*
Bronchogram	209
Surgical specimen	5
Postmortem specimen	5
Planogram	1
Total	220

Diagnosis. Table 5 shows the means by which the diagnosis of bronchiecta-

sis was confirmed in each of the 220 patients comprising this study. Two hundred and nine patients had bronchograms which showed the characteristic changes of bronchiectasis. In 5 instances the diagnosis was confirmed on examination of the pulmonary specimen postoperatively and in 5 other cases by postmortem examination. In 1 patient the diagnosis of bronchiectasis was verified by means of a planogram.

PULMONARY DISEASE LOCALIZATION. In Table 6 is shown the disease distribution found in this group. The localization of pulmonary involvement in each case was determined by the means previously described under "Diagnosis". One hundred and twelve patients (51%) had bilateral basal or extensive involvement. Of the group with only single lobe involvement, the left lower lobe was the site of localization in 45 patients (20%), while the right lower lobe was involved in 22 instances (10%). The combination of right middle and lower lobe disease was found in 18 cases (8%).

TABLE 6.—LOCALIZATION OF DISEASE IN 220 CASES OF BRONCHIECTASIS

Site	*Surgery*	*No surgery*	*Total*
Right upper lobe	1	2	3
Right middle lobe	5	3	8
Right lower lobe	6	16	**22**
Right upper & middle lobe	2	1	3
Right middle & lower lobe	12	6	18
Left upper lobe	4	1	5
Left lower lobe	21	24	**45**
Bilateral basal area	16	96	**112**
Right lung	1	0	1
Left lung	2	1	3
TOTAL	70	150	220

MEDICAL THERAPY. Sixty-six patients (30%) were hospitalized repeatedly prior to admission to the State of Wisconsin General Hospital. Often these periods of hospitalization were in sanatoria. The duration of hospitalization varied from weeks to many months. This obviously emphasizes the economic factors involved in this disease. One hundred and thirty-seven patients (62%) had postural drainage either prior to admission or following discharge. Sixteen patients (7%) received lipiodol insufflation as a means of therapy. All this number belonged to the first 5-year group (1938 to 1942). Twenty-one patients (10%) were treated with various sulfonamide preparations, while 47 (21%) received penicillin either by aerosol or the parenteral route. All the cases that received chemotherapy or antibiotics fell into the latter half of the period covered by this study (1943 to 1947).

TYPE AND RESULTS OF OPERATION. A breakdown of the 72 operative procedures performed on the 70 patients treated by surgery is shown in Table 7. There were practically twice as many left lower lobectomies performed (29) as any other single operative procedure. It is of interest that surgery on the right carried a much higher mortality than on the left (33%: 7%). One-third of the patients who had right middle and lower lobe lobectomy succumbed, as did one-third of the group who had right lower lobectomy. Only 2 of the 29 patients who had left lower lobectomies died.

SURGICAL DEATHS. Table 8 contains some of the pertinent data regarding the surgical deaths in this series. The over-all surgical mortality in this group was 12.5%. Again, it is strikingly apparent that resection on the right carried a much higher mortality than similar operation on the left.

matic. In no instance did any of the patients have as many symptoms or have any disability comparable to that which existed prior to operation. In 26 cases progress of the patient was not followed after recovery from the operation and discharge from the hospital. Twenty-seven patients were followed

TABLE 7.—RESULTS OF OPERATION IN 70 CASES OF BRONCHIECTASIS

Type of operation	*No. of operations*	*No. of deaths*	*Mortality*
Right upper lobectomy	1	0	0
Right middle lobectomy	7	0	0
Right lower lobectomy	6	2	33%
Right upper & middle lobectomy	2	0	0
Right middle & lower lobectomy	15	5	33%
Left upper lobectomy	4	0	0
Left lower lobectomy	29	2	7%
Right pneumonectomy	3	0	0
Left pneumonectomy	5	0	0
	72	9	12.5%

TABLE 8.—SURGICAL DEATHS DURING TREATMENT OF BRONCHIECTASIS

Year	*Age*	*Sex*	*Duration*	*Disease distr.**	*Operation†*	*Cause of death*
1938	38	M	8 yrs.	RMLL	RMLL	Postoper. shock
1940	54	M	2 yrs.	RMLL	RMLL	Postoper. cardiac collapse
1942	6	M	2 yrs.	RLL	RLL	Uncontrolled bleeding
1943	18	F	14 yrs.	BB	LLL	Bronchial obst. due to spill
1944	57	M	3 yrs.	RLL	RLL	Bronchopn. on 7 postoper. day
1944	43	M	25 yrs.	RMLL	RMLL	Pneumonia and mediastinal shift
1946	52	M	5 yrs.	RMLL	RMLL	Uncontrolled bleeding
1947	28	F	20 yrs.	BB	LLL RMLL '46	Pneumonia and lack respir. tissue
1947	51	F	3 yrs.	BB	RMLL	Pul. edema and spill

* See Table 6 for abbreviations.
† See Table 7 for abbreviations.

FOLLOW-UP. Although a detailed and comprehensive follow-up program is now in progress, an attempt was made at the time of this study to determine the degree and duration of improvement which occurred in the 61 patients surviving operation. All patients re-examined were improved or asymptomatic. In no instance did any of the patients have as many symptoms or have any disability comparable to that which existed prior to operation. In 26 cases progress of the patient was not followed after recovery from the operation and discharge from the hospital. Twenty-seven patients were followed from 1 to 3 years and 7 were followed from 4 to 6 years after operation. Only 1 patient was seen 7 years postoperatively.

NONSURGICAL CASES. Table 9 shows the results of an attempt to determine the reasons why 150 of the total 220 patients did not come to operation. In 98

cases (65%) no statement could be found in any of the hospital records relative to the consideration of surgical intervention for the demonstrated bronchiectasis. There was no reference made in these records as to the advisability of pulmonary resection and likewise no comment as to any contraindications to surgical therapy. In 16 cases (10%) the possibility of surgical treatment was noted; however, for various reasons (sinus surgery, allergy study, medical therapy trial, and the like)

TABLE 9.—REASONS FOR NO OPERATION IN 150 CASES OF BRONCHIECTASIS

Reason	*No. of patients*
Not stated (no comment)	98
Deferred (no comment)	16
Risk	24
Refusal	5
Died	7
TOTAL	150

operation was deferred. The majority of these patients were readmitted to the hospital but no further comment was made in regard to pulmonary resection. Twenty-four patients (16%) were denied operation because it was felt that the risk was too great. In 5 cases operation was recommended but the patient refused to accept this advice. Seven patients died while hospitalized on the Medical Service.

Comment. The outstanding clinical features found in this group of patients with proved nontuberculous bronchiectasis were cough, recurrent respiratory infections, and hemoptysis. The former was found in 100% and the latter 2 in approximately two-thirds of the cases. Occurring with less frequency but present in a significant number were clubbing of the digits, sinusitis, allergic manifestations, and fetor oris.

Singly, none of the observed signs is specific for bronchiectasis, but from this study one would conclude that the combination of the 3 most common features should justify at least a suspicion of this disease. With the concurrence of the additional signs, the clinical diagnosis of bronchiectasis should be made and maintained unless excluded by means of a bronchogram.

Fortunately, bronchography is a simple, nontraumatic, and readily available procedure. Since in many cases with even moderately advanced bronchiectatic disease the routine chest roentgenograms may be misinterpreted and read as negative, bronchographic study is essential for the verification of this diagnosis. If bronchiectasis is suspected in the patient presenting the syndrome described and a bronchogram is completed without delay, the presence or absence of bronchiectasis will be established and much of the past neglect of early diagnosis will be eliminated.

The pulmonary localization in this series is comparable with the results of similar studies appearing in the literature. The fact that over one-half of the patients had bilateral basal or extensive involvement suggests that there was a delay in diagnosis. This re-emphasizes the foregoing comments about past neglect in this area and the means for its correction.

An interesting feature of the surgical mortality in this study was the much greater hazard associated with resection on the right as compared with that on the left (33%: 7%). This series is not sufficiently large to warrant any specific conclusions regarding this finding but, if this observation is verified by data from other studies, it might have an important bearing on the advisability of pulmonary resection in selected cases. It at least provides a stimulus for re-evaluation of the technical–surgical possibilities which might be responsible for this difference.

Of importance relative to the reason why more patients in this series were not treated surgically is the fact that

the records of 76% of the medically treated cases contained no comment (or no evidence of reconsideration in 16 instances) concerning the possibility of surgical treatment for their proved bronchiectasis. Improved technique in thoracic surgery would not seem to be the crux of this problem, since only one-third of the medically treated cases fell into the first 5-year period of this study (1938–1942). It might be argued that the majority, if not all, of this group were not ideal candidates; thus surgical therapy was not recommended. It is difficult to concede this point, however, since a fair number were young and had localized disease. Granted that the remainder were less than ideal, if pulmonary resection had been considered at all, it might be expected that some comment or notation testifying to this consideration would be in evidence on the patient's record. None could be found.

The problem of neglect in bronchiectasis is quite similar to that of pulmonary tuberculosis in the rather recent past. The notable difference between them is the infectiousness of the latter which has resulted in a much more active and dramatic program of diagnosis and treatment. The means for specific diagnosis for both are well known and readily available. Their application, however, is dependent on the general practitioner's or internist's index of suspicion as to the presence of these diseases. Whereas routine chest roentgenograms are often diagnostic for tuberculosis, they may be of little aid in bronchiectasis. This fact places greater emphasis on the necessity for a keener awareness of bronchiectatic disease. The latter will be forthcoming with a closer scrutiny of the significance of its clinical features and the greater use of bronchography. If the diagnosis is made early, pulmonary resection is usually curative. It is the clinician's responsibility, not only to suspect and diagnose, but also fully to appreciate and utilize the advantages the thoracic surgeon offers these patients.

Summary. 1. Two hundred and twenty cases of proved nontuberculous bronchiectasis were analyzed as to the incidence of various clinical features and as to why surgical therapy was not utilized in the medically treated patients.

2. Cough, recurrent respiratory infections, and hemoptysis were the 3 most common characteristics in this series. Clubbing of the digits, sinusitis, allergic manifestations, and fetor oris were less frequent, but still occurred in 30% or more of the cases.

3. Delay in diagnosis can be corrected by treating the patient presenting the symptom complex described as a bronchiectasis-suspect and establishing or disproving the diagnosis by bronchography.

4. In this series pulmonary operation on the right carried a much higher mortality than similar operation on the left (33: 7%).

5. The records of 76% of the medically treated patients in this series had no comment regarding the consideration (or reconsideration in 10%) of pulmonary surgery as therapy for their proved bronchiectasis. The risk of survival postoperatively and refusal of operation by the patient were infrequent reasons for denial of surgical therapy.

6. The past two-fold neglect of bronchiectasis can be corrected if advantage is taken of the diagnostic and therapeutic facilities that are now available. The general practitioner and internist are in the position of greatest responsibility in this regard.

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TOXIC EFFECTS OF VARYING DOSES OF KEROSENE ADMINISTERED BY DIFFERENT ROUTES

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Kerosene intoxication has little importance in the petroleum industry. However, accidental ingestion of this hydrocarbon among young children occurs more frequently than is generally recognized. For example, of all the cases of poisoning treated in a large charity hospital in a recent year, kerosene intoxication was encountered more frequently than all other cases of poisoning combined[1].

It has been shown that the serious sequelæ following the ingestion of kerosene are due to pulmonary involvement. Whether the lung damage is due primarily to hematogenous transfer of the material or to aspiration has been debated. In a clinical and experimental study, Waring[6] emphasized the importance of aspiration of kerosene directly or by regurgitation from the stomach into the lungs. Nunn and Martin[5], in 1934, reported a series of 65 cases of kerosene poisoning and 7 gasoline poisoning cases in children. They concluded that the prognosis was in direct proportion to the amount of hydrocarbon entering the lungs. A similar opinion was expressed by Lesser, Weens, and McKey[4] following their roentgenological observations in patients and experimental studies with rabbits. More recently, however, Deichmann *et al.*[2] have placed considerable emphasis on the thesis that the characteristic pulmonary damage is due to blood-borne kerosene absorbed from the gastrointestinal tract. The present study was performed in a further attempt to determine the degree and extent of pulmonary injury produced by kerosene administration by different routes.

Methods. Kerosene was administered to a group of 38 dogs by the following routes: intragastric, intravenous, instillation into a segment of small intestine, intratracheal, and by stomach tube. In a series of 10 dogs with the dose of kerosene ranging from 5 cc. to 33 cc. per kg. of body weight, the animals were anesthetized with pentobarbital and the stomach exposed by means of an abdominal incision. Next the cardia was doubly ligated, and after the dose of kerosene was injected into the stomach by means of a needle and syringe, the laparotomy wound was closed. The same procedure was carried out on a group of 3 control animals where saline was substituted for the kerosene. In another group of dogs, 2 received intravenous doses of the oil of 0.25 cc. per kg. and 1 received 0.5 cc. per kg.

In 2 dogs prepared with a Thiry-Vella fistula, 50 cc. of oil was introduced into the segment of small bowel and allowed to remain for 4 hours. After about a week had elapsed the procedure was repeated and 4 days later the symptomless animals were sacrificed. In another series of animals, the hydrocarbon was injected into the trachea in doses ranging from 0.25 cc. to 1 cc. per kg. of body weight. Seventeen dogs were given kerosene by stomach tube in doses ranging from 2 cc. to 30 cc. per kg. of body weight. In these animals special measures were taken to prevent vomiting. First, the

vomiting center was depressed by the intravenous administration of 5 mg. per kg. of pentobarbital, following which the oil was given in an emulsified form in an aqueous solution of 0.5% chlorbutanol, which is recognized to have some local anesthetic action. Vomiting was prevented, in most instances, by such a procedure. Previously, small doses of morphine were found to be unsatisfactory in preventing late vomiting.

Observations were made on a group of 16 rabbits receiving kerosene intraperitoneally, by stomach tube, and by the intratracheal route. The intraperitoneal dose was 10 cc. per kg. of body weight. In 8 animals receiving the oil by stomach tube, the dosage range was from 15 cc. to 35 cc. per kg. of body weight. Six animals were given intratracheal doses ranging from 0.12 cc. to 0.50 cc. per kg. of body weight.

Results. The pulmonary injury produced by kerosene administered to dogs by various routes is shown in Figs. 1 to 4 inclusive. In most cases it was practically impossible to tell from the histological changes in the lungs which route of administration had been used, although vascular damage was most marked when the oil was given intravenously.

INTRAGASTRIC. In the dogs in which kerosene was introduced into the stomach by means of a syringe and needle, as described above, varying degrees of pneumonia occurred. How much of the lung involvement was due to kerosene is questionable. The fact that the survival time of 3 control animals was no longer than the average of the treated ones is evidence that the oil contributed little, if at all, to the death of the animals. Autopsy findings confirmed this. This observation is in agreement with that of Dragstedt and Mullenix[3] who reported a high percentage of aspiration pneumonia in dogs with an esophageal obstruction. While ligation of the cardia accomplished the purpose of excluding kerosene from the lungs through aspiration, nevertheless the results are clouded by the effects of the ligation *per se*. Consequently, more dependence is placed in the results on those animals receiving the oil by stomach tube with precautions taken to prevent vomiting.

INTRAVENOUS. Intravenous injection caused the most severe pulmonary damage, with almost complete obliteration of the architecture of the lung (Fig. 1).

INTESTINAL FISTULA. In the 2 animals receiving the oil by instillation into an intestinal fistula, there occurred a slight to moderate congestion of the lungs with considerable atelectasis. In some of the areas of collapse there was an increase in leukocytes, but there was no definite pneumonia. The intimal cells of the blood vessels showed swelling and vacuolization (Fig. 2). There was moderate to marked edema of the walls of some of the larger bronchi.

INTRATRACHEAL. When a dose of 1 cc. per kg. of body weight was injected into the trachea of one dog, death occurred in 10 minutes. Another animal receiving 0.5 cc. per kg. showed an acute bronchitis and an acute hemorrhagic pneumonia when sacrificed 4 hours after administration of the oil. Another animal receiving the same dose exhibited marked dyspnea 5 minutes after the injection. A half hour later the respiration was shallow and rapid, and continued so for several hours. On the following day there were marked depression and pronounced rales over both lungs. During the next 4 days the animal gradually improved except for rales over both lungs. On the 5th day after the oil was injected the animal was sacrificed. The severe pneumonia existing at that time is illustrated in Fig. 3. Similar lung lesions were produced in one animal receiving 0.25 cc. of the oil per kg.

STOMACH TUBE. Following the stomach tube administration of kerosene to a dog in which regurgitation was known to have occurred, there were marked vascular damage and bronchial

changes together with pneumonia, edema and congestion. Some of these changes are illustrated in Fig. 4. Significantly, there was 100% survival in animals receiving kerosene by the stomach tube route. In the animals that were sacrificed and autopsied from 1 to 18 days after receiving the oil, severe lung damage occurred only in those animals in which vomiting occurred. The gross and microscopic lung damage in such cases was not uniform in character, rather it was unevenly distributed and predominantly in the lower lobes, thus indicating aspiratory phenomenon rather than hematogenous transfer of the oil.

Table 1 summarizes the data in the dog experiments with respect to routes of administration, doses, survival time and autopsy findings.

A summary of the data on the studies in rabbits appears in Table 2. With intraperitoneal doses of 10 cc. per kg. of body weight the average survival time was 59 hours. Prior to death these animals were lethargic and depressed. Stomach tube doses of 35 cc. per kg. of body weight proved fatal in an average of four days, while doses of half this amount failed to produce death. Two animals receiving 25 cc. per kg. of body weight were sacrificed 7 days later. Although the lungs showed slight congestion and focal atelectasis, there was no pneumonia or bronchitis. This is considered particularly significant because of the inability of rabbits to vomit.

In those animals receiving the oil by the intratracheal route, the survival time was in direct relation to the size of the dose as indicated in Table 2. Death occurred after doses as small as 0.25 cc. per kg. of body weight.

Discussion. On the basis of the foregoing data it is difficult to conceive of a child drinking a sufficient quantity of

TABLE 1.—KEROSENE TOXICITY STUDIES IN DOGS

Number animals	*Route of administration*	*Dose cc./kg.*	*% Survival*	*Average survival time (hrs.)*	*No. autopsied*		*Microscopic pulmonary changes*				
					Gross	*Micro.*	*Congestion*	*Edema*	*Pneumonic*	*Bronchial*	*Vascular*
2	Intragastric	5	0	71	2	2	++++	+++	+	+	+
4	(Cardia ligated)	10	0	40	3	3	+++	++	+	++	++
3	"	30	0	29	3	3	++++	++	+	+	+
1	"	33	0	30	1	1	++++	−	−	+	+
3	"	control (saline)	0	41	2						
3	Stomach tube	2	100								
1	"	3	100								
1	"	5	100								
1	"	10	100								
2	"	15	Sacrificed		2	2	+	−	−	−	−
1	"	20	"		1	1	+++	+++	+++	+++	−
7	"	20	"		7	1	−	−	−	−	−
1	"	30	100		1	1	++	−	−	++	+
2	Intestinal (Thiry-Vella fistula)	10 (2 divided doses)	100 (1 sacrificed)								
2	Intravenous	0.25	50	60	1	1	+++	++++	++++	++++	++++
1	"	0.50	0	8	1	1	+++	++++	++++	++++	++++
1	Intratracheal	0.25	Sacrificed	-	1	1	+++	++	++++	+++	++
1	"	0.50	"		1	1	+++	+++	++++	++++	++
1	"	1.0	0	0.17							

TABLE 2.—KEROSENE TOXICITY STUDIES IN RABBITS

Number animals	*Route of administration*	*Dose cc./kg.*	*% Survival*	*Average survival time (hrs.)*	*No. autopsied*		*Microscopic pulmonary changes*				
					Gross	*Micro.*	*Congestion*	*Edema*	*Pneumonic*	*Bronchial*	*Vascular*
2	Intraperitoneal	10	0	59	2	2	++++	++++	−	+	+
2	Stomach Tube	15	100								
2	"	20	100								
2	"	25	Sacrificed		2	2	+		Focal atelectasis		
2	"	35	0	96	2						
3	Intratracheal	0.12	100								
2	"	0.25	0	60							
1	"	0.50	0	18	1						

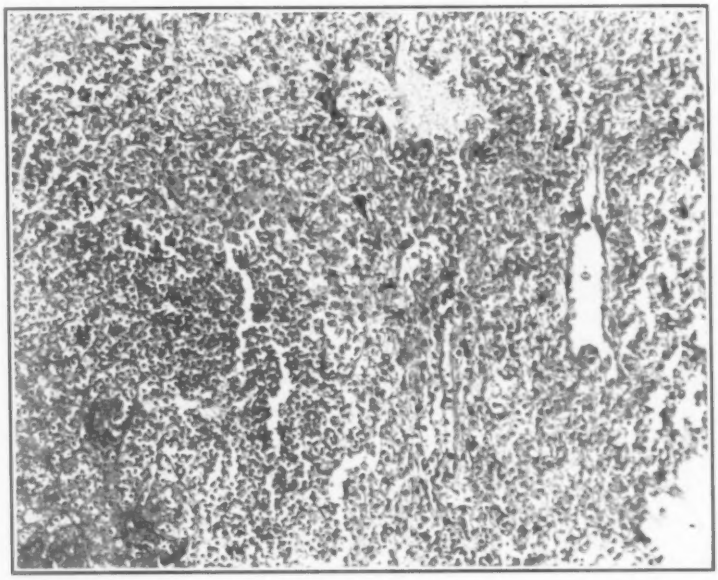

FIG. 1.—Severe suppurative and necrotizing pneumonia following intravenous injection of kerosene (× 150).

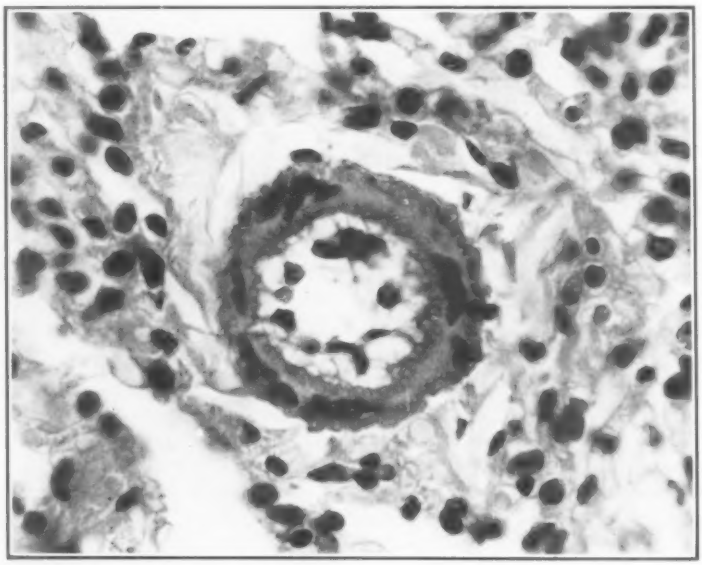

FIG. 2.—Endothelial cell swelling and vacuolization in a dog that received kerosene by way of the intestine (× 800).

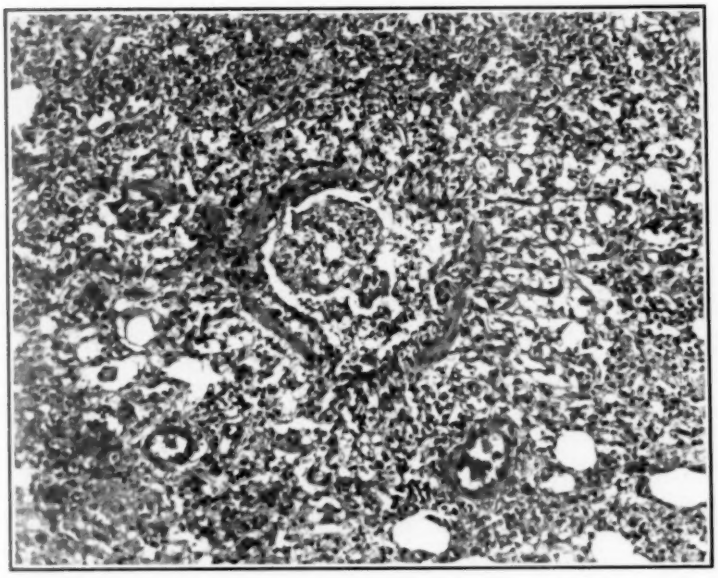

FIG. 3.—Organizing bronchiolitis with severe pneumonia following intratracheal injection of kerosene (× 150).

FIG. 4.—Marked edema of bronchial wall with leukocytic infiltration in a dog receiving kerosene by stomach tube. This change was also present in varying degrees in animals that received kerosene by intragastric, intratracheal, intravenous or intestinal administration (× 150).

kerosene to prove fatal only by absorption from the gastrointestinal tract. Our experimental results have more meaning if the doses used are based on a child weighing 50 pounds. In such a case, provided aspiration does not occur, a volume in excess of a pint would have to be swallowed in order to prove fatal. For a child to ingest this volume of an irritating liquid seems most unlikely. On the other hand, if slightly more than a teaspoonful were aspirated, severe pneumonia with an almost certain fatal outcome would result. Of primary concern, then, is the danger of aspiration rather than consideration of the possible absorption of the oil from the gastrointestinal tract. This view is in disagreement with that advanced by Deichmann *et al.*[2] The experimental observations of the present report, however, bring up no essential disagreement with the experimental observations which they reported.

If gastric lavage is resorted to, its primary intent should be a precautionary measure against regurgitation and subsequent aspiration rather than a safeguard against gastrointestinal absorption. Extreme care should be exercised during the washing, particularly in young children who have a recognized propensity for aspiration. Where the amount of kerosene ingested is known to be small and damage therefore unlikely, one might refrain from using the stomach tube, especially if there are no signs of regurgitation. Since the oil passes rapidly through the intestinal tract, a high cleansing enema would seem to be almost as effective, and at the same time would not involve the hazard of aspiration.

Summary and Conclusions. The toxic effects of varying doses of kerosene have been determined in dogs and rabbits. The following routes of administration were used: intragastric, intravenous, introduction into a segment of small intestine, intratracheal, intraperitoneal, and by stomach tube. Consideration of dosage and degree of lung damage clearly show that aspiration is the most serious and usual feature of kerosene poisoning as it occurs clinically.

We are obliged to Dr. J. I. Waring for his interest and suggestions in this study.

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SATIETY AS A FACTOR IN NUTRITION STATES: OBSERVATIONS ON MASS EXCHANGE*

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In studying problems of nutrition, many people feel that the relationship of the body weight to the balance between intake and output has been established. Interest therefore no longer resides in the demonstration that fat people eat too much and thin people eat too little but rather in the problem of why people eat as they do.

A great deal of thought has been devoted to the study of appetite which may be considered as the physiological complex having to do with why people start to eat. However, it might be equally pertinent to study the problem of why they stop eating when they do. Satiety may be considered as the limit of tolerance, or, perhaps, comfort, resulting from the total physiological load due to food intake. We have been interested in trying to demonstrate some of the individual components of this load and to suggest how they might conceivably contribute to the development of the sensation "satiety". It also becomes desirable to observe these components in persons of different states of nutrition in order to note any significant differences.

In this study we are trying to visualize the physiological stresses and strains which are thrown on the body in the course of 24 hours of intake and output. As indices of the load we are comparing, first, the mass of intake to the mass of residual body. What is the gross load of material thrown into the melting pot in relation to the size of the pot? Second, as one measure of the stresses and strains involved in getting rid of this intake load we are using the weight of the urine output in its relation to body mass. These indices quite obviously fail to supply the complete picture of mass balance, but they have the merit of being based on direct observations. We also include data on the caloric intake for 3 purposes: (1) to compare and contrast the familiar data for calories per kilo of body weight with the data for grams per kilo of body weight, (2) to show the additional strains involved in the rates of body weight change produced at the several levels of calories per kilo, and (3) to show the independence of the ratios for mass load and for energy load.

Observations. Observations are reported on 16 patients between the ages of 18 and 58. There were 14 women and 2 men. These patients were studied on the metabolic ward for periods varying from 2 weeks to 6 months. The data for each patient were arranged as shown in Table 1. Each horizontal line represents the average of the daily observations for the period indicated, usually 6 to 7 days. It should be noted that the entire periods of study were not analyzed for all patients. In cases which ran 3 to 6 months, 1 or 2 average weeks of each month were analyzed. The exact number of periods studied and the total length of the study are indicated for each patient in the subsequent summary charts. It seemed unnecessarily burdensome to calculate each week of a long series where the variations were relatively slight. However, the rather marked over-all weight changes in some patients required sampling of the data for each month.

* Presented at the meeting of the American Clinical and Climatological Association, October 16, 1950.

The body weight is that of the first day of the period. The average weight change per day, column 5, was obtained by dividing the total weight change for the period by the number of days.

The intake columns show the average weights per day of everything taken by mouth. The adjacent columns show the extreme ranges of daily variation. Column 9 shows the ratio of intake to initial body weight for that week expressed in per cent. A change in the decimal point gives grams intake per kilo. The output columns record the daily urine weights in a manner comparable to the intake data. Columns 14 and 15 show the caloric intake. The several columns are averaged at the bottom of the table.

(2) thin patients increasing weight, (3) obese patients losing weight.

The patients who were maintaining their weights were further arranged in 3 groups based upon their nutritional status: (1) those of normal weight, (2) those under weight, (3) those over weight.

The data for 3 patients of normal weight appear in Table 2. The first few columns give the over-all statistics of each patient. The pertinent observations appear in the last 8 columns.

The summary shows that these patients who were only 3% below ideal

TABLE 1. METABOLIC DATA IN A NORMAL PATIENT*

Week	Body weight		Gm. per day	Intake				Urine				Cal.	
	Initial	Change		Ave. daily	Max.	Min.	per kilo	Ave. daily	Max.	Min.	per kilo	Total	per kilo
11/17	20‡† 62.6	−.9	−90	3.16	4.35	2.36	5.1	1.81	2.78	1.11	2.9	2360	38
27	12‡3 61.7	0	0	3.02	4.00	1.95	4.9	1.59	2.41	.91	2.5	2450	40
4	10 61.7	+.2	+30	3.34	4.05	2.52	5.4	1.99	2.71	1.28	3.2	2410	39
11	17 61.9	+.6	+90	3.49	4.04	2.87	5.6	2.01	2.59	1.65	3.2	2340	38
18	23‡† 62.5	−.7	−110	2.78	3.61	2.08	4.5	1.44	1.92	1.04	2.3	2400	38
24	61.8										2.9	2390	39
Ave.			−20	3.17			5.1	1.78					

Age 23 Height 63‡ Ideal Wt. 58.5

* Values are in kg. unless specified.

† Days other than 7.

From Table 1, it may be seen that the average daily weight change of this patient was small, only 30 gm. per day for 5 weeks on a diet of 2390 calories. Her average intake per day was 3170 gm., which is 51 gm. per kilo, or 5.1% of her body weight. The urine output averaged 1780 gm., which is 29 gm. per kilo, or 2.9% of the body weight. Although the maximum and minimum daily values for intake and urine weight show considerable variation, the weekly averages are rather uniform. Such a chart was made for each patient. The subsequent tables are constructed from the summary lines of these individual charts.

The observations on the 16 patients may be grouped under 3 main headings: (1) patients maintaining weight, weight had negligible weight changes in the average 5 weeks studied. The intake per day averaged 5.1% of the body mass; the urine, 2.8%. These patients required 35 calories per kilo for maintenance. A comparison of the 35 calories per kilo with the 51 gm. intake per kilo gives 0.7 calorie per gram. This figure is a rough measure of the concentration of the intakes employed and provides an interesting comparison with the other diet programs reported below.

The data for 2 undernourished patients who were approximately maintaining weight are shown in the upper part of Table 3.

These patients who were 22% underweight gained only 30 gm. per day for the 4 weeks studied. The intake ratio

TABLE 2 METABOLIC DATA IN 3 PATIENTS OF NORMAL WEIGHT*

			Body weight						Rate body wt. change	Intake		Urine		Calories	
Pt.	Age	Total wks.	Ideal	Initial	% Deviation	Final	Total change	Wks. anal.	gm.	Wt.	per kilo	Wt.	per kilo	Total	per kilo
B	23	5	58.5	62.6	+7	61.8	−.8	5	−20	3.17	5.1	1.78	2.9	2390	39
C	33	14	60.8	54.9	−10	56.1	+1.3	6	+60	2.90	4.8	1.64	2.6	2230	39
J	31	9	60.9	57.8	−5	57.2	−.6	4	−20	3.09	5.3	1.84	3.2	1710	29
Ave.					−3			5	0	3.05	5.1	1.75	2.9	2110	36

* Values are in kg. unless specified.

TABLE 3. METABOLIC DATA IN 2 UNDERNOURISHED PATIENTS AND 3 OBESE PATIENTS*

WEIGHT MAINTENANCE—UNDERWEIGHT

			Body weight						Rate body wt. change	Intake			Urine			Calories		
Pt.	Age	Total Wks.	Ideal	Initial	% Deviation	Final	Total change	Wks. anal.	gm./day	Wt.	per kilo	per kilo ideal	Wt.	per kilo	per kilo ideal	Total	per kilo	per kilo ideal
H	18	8	58.9	48.5	−18	48.5	0	4	0	2.48	5.1		1.22	2.5		1800	37	
F	39	4	73.2	55.9	−25	58.7	+2.8	3	+60	3.39	5.9		1.57	2.7		2550	45	
Ave.					−22			4	+30	2.94	5.5		1.40	2.6		2180	41	

WEIGHT MAINTENANCE—OVERWEIGHT

Wz	42	2	69.5	149.9	+110	148.4	−1.4	2	−110	4.62	3.1	6.6	2.68	1.8	3.8	2920	19	42
W	38	2	61.4	107.0	+74	104.4	−2.6	2	−250	4.08	3.8	6.7	2.49	2.3	4.1	2500	24	41
N	44	2	61.6	94.7	+54	93.4	−1.3	2	−110	4.53	4.8	7.3	2.60	2.7	4.2	2450	26	40
Ave.					+81			2	−160	4.41	3.9	6.9	2.59	2.3	4.0	2620	23	41

* Values are in kg. unless specified.

is 5.5%; the urine ratio, 2.6%. The calories were 41 per kilo, which may account for the slight weight gain. The calorie per gram ratio of 0.71 suggests that the food types were similar to those in the normal group.

It is quite difficult to get reliable data with reference to the maintenance requirements of obese patients under hospital conditions. The best approximation could be obtained by fixing diets of 2500 to 3000 calories and noting the rate of weight loss. The observations for 3 obese women are reported in the lower section of Table 3.

These women averaged 81% overweight and they lost 160 gm. per day on diets of 2500, 2500, and 2900 calories respectively. The mass ratios show considerably more individual variation than in the preceding groups but they average 3.9 for intake and 2.3 for urine. The patients received 23 calories per kilo. Reference to the columns showing actual weight of intake indicates that the intakes really were quite large, averaging 4400 gm. per day, which is nearly 50% above the normal group. The calorie per gram intake ratio is only 0.60, which points to an increase in the water intake of these obese patients.

In previous reports on obesity, the concept of relating observed data to the theoretically ideal weight of the patient has been employed in the belief that the ideal weight gives an approximation of the functioning tissues of the body apart from the masses of relatively inert fat. This calculation has been made also in this study. The recalculated data became: intake 6.9%; urine 4.0%; and calories per kilo 0.41.

It will be noted that the thin patients had ratios quite comparable to the normal patients, whereas the obese patients had ratios slightly lower. This observation might indicate that satiety

had not really been attained in these obese patients even by diets which were 20% or more higher than the normals but which were inadequate to prevent a fair rate of weight loss. The drop in the calorie per gram ratio to 0.6 likewise points to the lack of satiety and to the increase in water intake.

The information on 6 thin people who were gaining weight is summarized in Table 4.

The results on 4 obese patients are shown in Table 5.

The patients were women between 38 and 58 years. They were initially between 71 and 180%, average 133%, overweight. They were 25 to 119%, average 99%, overweight at the conclusion. The average weight loss was 32 kg. The total periods of study were 6 to 26 weeks. The first patient had a second period of study 1 year after her first admission. At this second entry, her weight was 72 kg. less than at the first. She is, therefore, included as a separate entry. The table shows the rapid rate of weight loss obtained by diets of 2 to 9 calories per kilo. The actual weight of intake was quite high, yet the ratio was only 2.7% of the mass. This was about 1/2 of the ratio for normals. Likewise, the ratio for urine was low. When these data are recalculated on the basis of the ideal weight, or possible functioning tissue, the ratios resemble very closely the ratios observed in normal people. We have never before appreciated the relatively enormous quantities of water which these obese people ingest. The relatively normal urine output reflects the high rate of weight loss in insensible perspiration which, of course, would be expected from the known high levels of metabolism of these obese people. In this series, the average of 4 calories per kilo, when compared with the weight of 54 gm. per kilo, shows a ratio of 0.08 calorie

TABLE 4. METABOLIC DATA IN 6 THIN PATIENTS GAINING WEIGHT[a]

			Body weight						*Rate body wt. change*	*Intake*		*Urine*		*Calories*	
Pt.	*Age*	*Total wks.*	*Ideal*	*Initial*	*% Deviation*	*Final*	*Total change*	*Wks. anal.*	*gm./day*	*Wt.*	*per kilo*	*Wt.*	*per kilo*	*Total*	*per kilo*
St	22	4	57.2	45.6	−20	50.7	+5.1	2	+200	2.88	6.1	1.39	2.9	2740	58
Ch	32	3	56.7	38.6	−32	44.5	+5.9	3	+260	3.10	7.6	1.43	3.5	2850	70
Ho	35	6	71.4	39.0	−45	58.9	+19.9	6	+410	4.31	8.7	1.64	3.3	5070	103
A	23	14	59.9	41.4	−31	53.7	+12.3	8	+130	3.42	7.4	1.84	4.0	2700	59
Ja	24	12	54.9	40.8	−26	53.0	+12.2	7	+130	3.02	6.8	1.45	3.2	3120	69
Co	22	4	54.0	43.2	−20	47.6	+4.4	3	+160	2.81	6.3	.96	2.1	3100	69
Avr.					−29		+10.0	5	+220	3.26	7.1	1.45	3.2	3260	71

[a] Values are in kg. unless specified.

There were 5 women and 1 man between the ages of 22 and 35. They were 20 to 45%, average 29%, underweight at the start. They were between 3 and 21%, average 12%, underweight at the end of the periods of study. The average weight gain was 10 kg. The total periods varied from 3 to 14 weeks with an average of 7 weeks. As shown in the tables, the strains thrown on these patients were considerable. The mass intake averaged 7% of the body mass, an increase of 40% over the normal group. The urine output, however, was but slightly higher than the normal. It may be noted that these patients gained an average of 230 gm. per day while taking 71 calories per kilo, approximately twice the normal intake. Since the calories per kilo and the grams per kilo were both 71, the intake contained approximately 1 calorie per gram. This value indicates that the intake was a third more concentrated than on the maintenance programs.

per gram. This intake concentration is about 1/9 of that of the normal group or 1/12 of the concentration on the fattening regimen.

Discussion. What do all these data mean with reference to body maintenance? The data on normal persons may be interpreted to suggest that an intake load of 5% of the body mass is handled with comfort and that perhaps this loading rate is a component of the sensation of satiety. Certainly these people could have eaten more or less, yet they did just what the vast majority of persons normally do, that is, they maintained their average weights from day to day. The urine load was likewise fairly constant on the average. This is also remarkable since additional water was freely available. Perhaps this too is a satiety factor in the sense that a fairly uniform metabolism results in a fairly constant production of waste products requiring excretion and a fairly constant percentage of water retained in the body.

The thin people who maintained their weights had ratios quite comparable to the normals. Since these people attained satiety, perhaps these data emphasize the preceding values. Weight maintenance was not attained in the obese group. Although the ratios resemble the preceding, they are slightly lower. The low ratio of calories to grams of intake, 0.58, also suggests that these patients were drinking a lot more water than the other groups, perhaps in an attempt to get the desired mass effect.

Anyone who has watched thin people in their efforts to gain weight recognizes the overloading and the acute distress which they endure. These data suggest one measure of their physiologic load. It takes genuine determination and grit to take in a body weight of material every 12 to 14 days. The rate of weight change gives another clue to the metabolic stresses involved. Why the urine shows so little change in ratio is hard to understand, although the higher percentage of the relatively dry fatty foods and a low water intake would account for some of the apparent discrepancy.

The fat people on reduction programs show the expected low ratio of gross intake to gross weight. The relatively enormous water intakes of these people have been noted. When the data are recalculated on the basis of ideal weight, we find that the masses of intake and of urine output approximate the ratios found for normal people. Is it possible that this excessive water intake represents a subconscious attempt of the patient to attain at least the mass components of satiety both with reference to intake and urine output?

TABLE 5. METABOLIC DATA IN 4 OBESE PATIENTS LOSING WEIGHT*

			Body weight						*Rate body wt. change*	*Intake*			*Urine*			*Calories*		
Pt.	*Age*	*Total Wks.*	*Ideal*	*Initial*	*% Deviation*	*Final*	*Total change*	*Wks. anal.*	*m./day*	*Wt.*	*per kilo*	*per kilo ideal*	*Wt.*	*per kilo*	*per kilo ideal*	*Total*	*per kilo*	*per kilo ideal*
Jac	39	19	61.2	171.2	+180	134.0	−37.6	6	−310	2.43	1.6	4.0	1.10	.7	1.8	390	3	6.
Jac	40	16	61.2	105.1	+71	76.9	−28.2	4	−140	3.10	3.5	5.1	2.05	2.3	3.3	780	9	13.
Re	58	26	70.9	196.4	+177	146.7	−49.7	7	−310	4.25	2.5	5.9	2.39	1.6	3.4	350	2	5.
Wa	38	6	61.4	133.6	+119	123.3	−11.3	5	−320	3.06	2.4	5.0	1.21	.9	1.9	530	4	9.
Cz	42	17	69.5	150.5	+116	117.0	−33.5	4	−360	4.96	3.7	7.1	3.47	2.6	5.0	590	4	9.
Avg.					+133		−32.1	5	−290	3.56	2.7	5.4	2.04	1.6	3.1	530	4	8.

* Values are in kg. unless specified.

Conclusions. Attention has been drawn to the magnitude of daily mass exchange.

The possibility is considered that the rate of mass exchange is one additional component of the sensation of satiety. Perhaps an exchange which is approximated by an intake of 5% and a urine weight of 3% of the body mass promotes satiety.

Some of the stresses encountered by thin people in their attempts to gain weight are described, notably the 40% increase in rate of mass intake.

The possible relationship of mass exchanges of obese persons during reduction periods to satiety are mentioned.

If the rate of change of body mass constitutes one factor in the sensation of satiety which in turn stops food intake, it becomes more understandable why thin people stay thin, fat people stay fat, and the ordinary person changes his weight but little from month to month.

WHIPPLE'S INTESTINAL LIPODYSTROPHY: ITS RELATIONSHIP TO THE RHEUMATIC STATE*

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In 1907 Whipple[25] described a disease which appeared to represent a new clear-cut pathologic entity to which he gave the name intestinal lipodystrophy, a disease characterized by nutritional failure in association with arthritis. Since that time a number of cases have appeared in the literature which either have been labelled as Whipple's intestinal lipodystrophy or have been proved to be such by biopsy or at autopsy. However, if the criteria of the pathologic findings of Whipple are applied, it would appear that only 22 cases have been described[1,2,6-9,11-17,20-25].

We wish to add 4 more instances of intestinal lipodystrophy to those already reported. Furthermore, it is our intention to add still another theory regarding the possible etiology and pathogenesis to those which have already appeared. This will require emphasis upon clinical and pathologic findings which generally have been considered to be accidental and unrelated to the intestinal disease.

We also wish to interpret the clinical picture of Whipple's disease as derived from a study of all reported cases.

Of the 22 acceptable cases of Whipple's disease which have been reported, only 2 have had an ante-mortem diagnosis. The first of these was by Oliver-Pascual[17] in 1947, and the second by Hendrix, Black-Schaffer, Withers and Hankler[11]. Three of our 4 patients were diagnosed at operation and by biopsy.

Case Reports. Case 1. A 43-year old white laborer was admitted to the Vanderbilt University Hospital February 2, 1943, complaining of weakness, fatigability, breathlessness, and post-prandial epigastric distress. Six years before admission he began to have "rheumatism" affecting the hips, knees, ankles, shoulders, elbows, wrists, fingers, and back. There was never redness or swelling of the joints and there were asymptomatic periods lasting a month or two. At times there were "kernels" over the involved joints. After dental extractions the arthritis gradually diminished 4 years after its onset. Two years before admission he became aware of the ease of fatigue and breathlessness. He could do no more than a half day's work. He also noted a nonradiating pain and tenderness in the costovertebral angle area. At first the breathlessness was troublesome only upon severe exertion but the dyspnea and his weakness gradually increased in the 4 months before hospitalization. Palpitation was present at times upon exertion. He lost 10 to 15 pounds in weight during 1942. Two months before hospitalization he had 4 mild chills with fever and vomiting within a period of 3 weeks. He also noted an epigastric burning or gnawing pain and heartburn an hour after meals, partially relieved by soda. For 4 weeks before admission he had a cough productive of a small amount of mucoid sputum

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and some retrosternal tightness. For 3 weeks before admission he had epigastric tenderness, anorexia, and paresthesias of the feet.

His *past history* revealed "pneumonia" 3 times in childhood, "heartburn" relieved by soda periodically "all his life," and nocturia of 4 to 5 times each night for the past 2 or 3 years.

Physical Examination. There were marked undernutrition, pigmentation limited to the exposed areas, and slight cheilosis. The right epitrochlear, inguinal, axillary, and cervical nodes were enlarged and firm; some were 2 cm. in length. The conjunctivae were pale. The tongue was pale, with generalized papillary atrophy. He was edentulous. Though the left upper chest was flattened, the expansion was fair. Dullness and suppression of the breath sounds were noted in this area. The heart was normal. The abdomen was soft and free of abnormal masses. Blood pressure ranged from 80 to 100 systolic and 50 to 60 diastolic.

A chest film showed only moderate fibrosis of the left upper lung area. A film of the abdomen and a gastro-intestinal series were negative.

Laboratory Findings. Urinalyses showed specific gravities up to 1.020 and occasional white and red blood cells. Blood studies showed: Hgb. 8 gm.; RBC 3.83 million, P.C.V. 22, MCV 57.4 cuμ and MCHC 36.3%, E.S.R. 4 mm.; WBC 8000, with an eosinophilia of 10 to 13%; Kahn test, negative; NPN 30 mg.; sugar 80 mg.; CO_2 64.3 vol.%; chlorides 93 mEq./L; serum protein 5.56 gm. (albumin 2.91 and globulin 3.65); Wilder test—serum Na 118 mEq./L before the test, 124 mEq./L after the test (control 135 mEq./L); water test—10:30 p. m. to 7:30 a. m. 530 cc., 1 hr. 130 cc., 2 hr. 70 cc., 3 hr. 300 cc., 4 hr. 560 cc., 5 hr. 195 cc. The stools were negative for occult blood and parasites. The metabolic rate was —6%.

Course. During the 22 days in the hospital the temperature varied from 97.6 to 99°F. A diagnosis of hypochromic anemia and possible Addison's disease was made. He was discharged on therapy consisting of ferrous sulfate and sodium chloride, 4 gm. 3 times daily.

The patient was seen in the Outpatient Clinic on March 23 and April 6. His weight on these dates was 149 and 144 pounds, respectively. The blood pressure on the latter date was 85/50.

Second Admission. April 13, 1943. Though subjectively better, he still complained of anorexia, weakness and ease of fatigue.

The physical findings were unchanged.

Laboratory Findings. The only change of significance was in blood chlorides, which were 85 mEq./L. Free hydrochloric acid was present in the gastric content after histamine.

Course. Upon the supposition that he had Addison's disease, he was given 5 mg. of desoxycorticosterone daily intramuscularly. His blood pressure rose to 100 to 110/60 to 75. He was discharged on May 1.

On May 21, after having received desoxycorticosterone 5 mg. daily until May 19, he was feeling better, noting his best strength 3 hours after the injections. He received no more of the steroid.

On July 20 he complained of increasing constipation and abdominal distention. A hard mass was palpable in the upper abdomen which did not move upon respiration. Hospitalization was refused. A roentgenogram following a barium enema on July 29 revealed a normally functioning colon and terminal ileum.

Third Admission. On August 2, 1943, he was readmitted because of progressive weakness, nausea, abdominal distention, and edema of the ankles. The only significant changes were: a soft blowing murmur in the pulmonic area; occasional premature contractions; distention of the abdomen with signs of ascites and of venous collateral circulation; a questionable mass in the right upper quadrant; large thrombosed external hemorrhoids; pitting edema of the ankles; and tenderness of the gastrocnemius muscles.

The gastro-intestinal Roentgen series showed pressure upon the duodenum, and at 4½ hours the small bowel showed "irritability", with rapid movement of the barium along the tract.

Laboratory Studies. The findings were: a negative urine, Hgb. 7.5 gm., RBC 4.0 million, P.C.V. 33% (improved after transfusions); WBC 8200; E.S.R. 10 mm.; negative blood Kahn. Blood chemical tests: normal values for NPN, sugar, chlorides, uric acid, vitamin C, phosphorus, alkaline phosphatase, acid phosphatase, and cholesterol. The serum protein was 4.77 gm. (albumin 2.38 and globulin 2.39 gm.). The serum sodium was 132 mEq./L. Oral glucose tolerance test: fasting 74, 30 min. 107, 1 hr. 107, 2 hrs. 82, 3 hrs. 71 mg. Intravenous glucose tolerance test: fasting 80, 30 min. 130, 1 hr. 110, 2 hrs. 80 mg. Vitamin A absorption test: 4 hrs. 20, 8 hrs. 20, 12 hrs. 32, 16 hrs. 30, 20 hrs. 30, 24 hrs. 30 I.U. Achlorhydria was present even after histamine. Bleeding time was 1¾ minutes; clotting time (tube method) 1 minute. Liver function tests: icterus index 2; BSP 2% retention in 30 min.; hippuric acid excretion test, 11.79 mg. benzoic acid in 1

hr.; galactose tolerance test, sugar only in 1 hr. (total excretion 0.58 gm.). The metabolic rate was −18%, specific dynamic action test −6%. Ascitic fluid: specific gravity 1.014, red blood cells 273 per c.mm., white blood cells 2 per c.mm., protein 3.14 gm., culture sterile, guinea pig inoculation negative results. A skin biopsy showed melanin in the deep layers.

Course. He was discharged on August 25, after receiving paracenteses and transfusions.

On September 17, he appeared in the Outpatient Clinic, having improved in strength and appetite. The abdomen had been tapped 2 weeks before. On November 19, he was unchanged, having had 8 paracenteses in the interval.

Fourth Admission, Jan. 15, 1944. Two weeks before he had developed "flu". Since then he was troubled with cough, anorexia, malaise, generalized pains, and pain referred high in the epigastrium. Constipation was present. He had had epistaxis, rectal bleeding, and "red spots" in the skin.

Examination. He was emaciated. There were dullness and crepitant rales at the lung bases. The heart was not enlarged; there was a question of a pericardial friction rub. Blood pressure was 85/65. The abdomen was distended and tender. Temperature was 100° F. The blood showed Hgb. of 8.3 gm., RBC of 3,610,000, and WBC of 10,000.

Course. He expired 5 hours after admission with the clinical interpretation that he had died of hepatic cirrhosis with cholemia and uremia, the latter accounting for the peritonitis and pericarditis.

Necropsy. The abdomen contained 5000 cc. of a browish-yellow fluid having a fecal odor and loculated in the upper abdomen under the liver and in the pelvis. The serosa was thickened, edematous, and greenish black. There was thick purulent exudate in the above areas.

The right pleural cavity contained 100 cc., and the left 50 cc., of yellowish-green fluid. Dense pleural adhesions obliterated the upper right and the lower left pleural spaces. The remaining pleural surfaces were edematous, dull, and had flecks of fibrin. Some areas of bronchopneumonia were noted.

The pericardial space was obliterated by dense fibrous adhesions. The myocardium was brown, soft, and flabby. The mitral valves showed numerous opaque, white nodules 1 to 2 mm. in diameter with an absence of the leaflet edge. The chordae tendineae were thickened and shortened. The papillary muscles were not remarkable. The remaining valves were normal. The slightly sclerotic coronary arteries were patent throughout.

The esophagus, stomach, and pyloric ring were normal. "In the duodenum just distal to the pyloric ring were seen patches of dusky grey discoloration and the wall was thickened. There was diffuse dilatation of the lacteals with a yellow, rather milky fluid.

"The mucosa of the small intestine showed numerous petechiae and marked edema. The wall was considerably thickened; the serosa was covered with a greenish-black fibrinous exudate. The midportion of the appendix was occupied by a thin, veil-like, blackish membrane which had a perforation about 1 cm. in diameter which extended into the cecum. . . . The large intestine showed edema, hemorrhage with serosal exudate as above. The markedly enlarged mesenteric nodes were diffusely yellow with a firm rubbery consistency. The cut glands exuded an enormous quantity of fatty material."

The pancreas, adrenals, and genito-urinary organs were normal. Except for a fibrinopurulent greenish-yellow exudate over the liver and irregular thickening of the splenic capsule, these organs were normal.

Microscopic Findings. *Heart.* The section omitted the epicardium. The only myocardial change was a moderate separation of the bundles.

Lung. Section of an isolated nodule proved this to be an early abscess. The central alveolar walls were destroyed and others were greatly distended with fibrin, polymorphonuclear leukocytes, and cellular debris. There were no other significant findings.

Gastro-intestinal Tract. The mucosa was autolyzed generally. The tips of many of the markedly enlarged villi were quite necrotic. The lamina propria was packed with lipoid-laden mononuclear foam cells superficially and was riddled with large, clear vacuoles about which an occasional giant cell was seen. The submucosa showed slight edema. The serosal surface showed a small amount of fibrin with polymorphonuclear leukocytes as well as a few foreign body giant cells. There was active proliferation of fibroblasts as well as endothelium. There was a moderate amount of round cell infiltration predominantly of the lymphocytic type in the deeper layer of the peritoneal exudate. A section of the appendix showed no mucosal involvement, but the peritoneal reaction was similar to that just described (Fig. 1).

Mesenteric lymph node. The capsule was normal. The node was riddled by many clear vacuoles, some of which were large enough to be visible to the naked eye. Numerous multinucleated cells were seen about these

vacuoles. A few lipoid-laden foam cells and numerous plasma cells as well as lymphocytes were seen in the sinusoids. A few polymorphonuclear leukocytes were seen in the subcapsular sinusoids (Fig. 2).

The serosal surfaces of other abdominal organs also showed an organizing fibrinopurulent exudate.

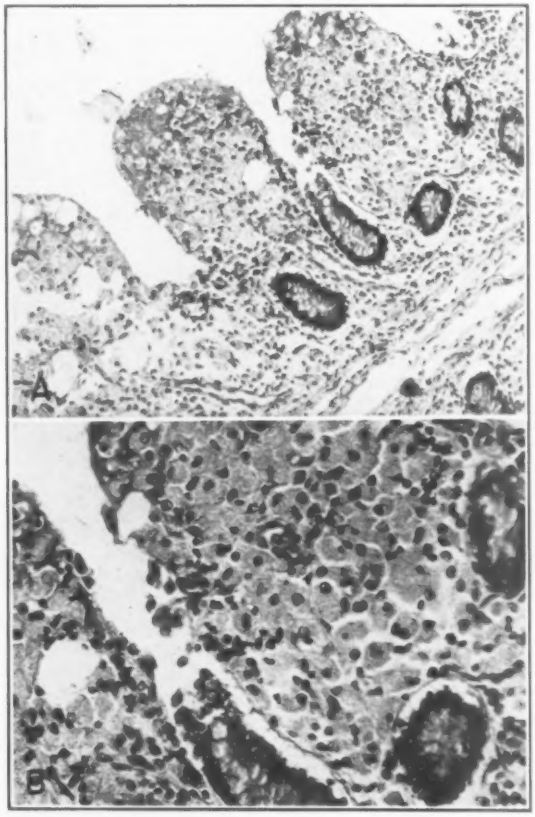

FIG. 1.—A The mucosa of the gut, from Case 1, showing thickening of the villi due to the presence of large mononuclear cells and dilated endothelial lined spaces. (X 150)

B The large macrophages filled with phagocytosed material. The tissues had been fixed with Zenker's solution prior to diagnosis and stains for fat were not possible. (X 300)

Kidneys. There was considerable cloudy swelling of the epithelial cells of the convoluted tubules. The blood vessels showed slight sclerosis, though the lumina were still patent.

The anatomical diagnoses were: 1) intestinal lipodystrophy of Whipple, 2) acute generalized fibrino-purulent peritonitis, 3) gangrenous appendix, ruptured, 4) chronic adhesive pericarditis, 5) chronic valvulitis, rheumatic, 6) early lung abscess, and 7) pyothorax, bilateral.

CASE 2. A 13½-year old white female was admitted to Vanderbilt University Hospital on Jan. 20, 1945, with complaints of weakness and loss of weight. Though she had always been frail, there was no specific complaint until Nov. 1, 1944, when she began to have fever and swelling of the interphalangeal joints. Within a short time an erythematous rash appeared over her acral joints and elbows and she began to have abdominal pain. This was followed by the development of facial erythema and generalized lymphadenopathy. She continued to have a low-grade fever and lost weight. After 3 weeks of illness she was admitted to a hospital in another city.

There she weighed 81 lb. She had a "butterfly" erythema of the face and erythema of the elbows and hands. There was fusiform swelling of the interphalangeal joints. The blood pressure was 100/50. The laboratory findings were as follows: urine 1+ albumin; RBC 3.5 million; Hgb. 55%; WBC 6000. Blood cultures yielded no growth. Films of the chest were negative. The electrocardiogram was interpreted as indicating myocardial damage.

Her temperature ranged from 100 to 103° F. After 3 weeks she complained of visual disturbance and the fundi showed exudate without hemorrhage. There was a gradual return of vision. After 4 weeks an inguinal node was removed. Bleeding occurred into the wound and she began to develop decubital ulcers. At this time a generalized brownish pigmentation appeared though the erythema of the face disappeared. Also at about the same time she developed a sore mouth. Abdominal and chest pain were present and of increasing severity. She had no diarrhea. Treatment included transfusions.

She gradually lost ground and was transferred to Vanderbilt University Hospital 80 days after the onset of her illness.

Physical Examination. She appeared cachetic, with deep brownish pigmentation of the skin generally, darker at the site of the old skin lesions. Erythema was present over the elbows, and also over the pressure points of the sacrum. The biopsy wound was wide open. There were small shotty glands in the cervical, axillary, and inguinal areas. The optic fundi showed large patches of yellowish exudate without hemorrhage. The buccal mucosa was extensively ulcerated and covered with whitish exudate. The lungs were clear; the heart was overactive. The abdomen was slightly distended and had a doughy resistance without any palpable viscera. There were contractures of the elbows and fusiform swelling of the fingers. The joints were not painful on motion and were only slightly tender to pressure.

Films of the chest showed irregular densities in the lung bases. Films of the joints showed only soft tissue swelling.

The electrocardiogram showed low voltage and an absence of or inversion of the T waves.

Laboratory Findings. Blood findings were: Hgb. 12.5 gm.; RBC 3.6 million; WBC 3-19,000; serum protein 5.18 gm. (albumin 2.56 and globulin 2.62). Urinalysis showed irregularly traces of albumin and sp. gr. 1.012 to 1.026. Glucose tolerance test: fasting 77, 30 min. 107, 1 hr. 108, 2 hr. 108, 3 hr. 87, 4 hr. 92, 5 hr. 81 mg. Vitamin A absorption test: fasting 58, 5 hr. 59, 9 hr. 46 I.U.

A nodule from the sheath of the median nerve and a segment of the erythematous skin were removed for biopsy. These showed chronic inflammatory changes not characteristic of any specific lesion.

Course. The temperature ranged from

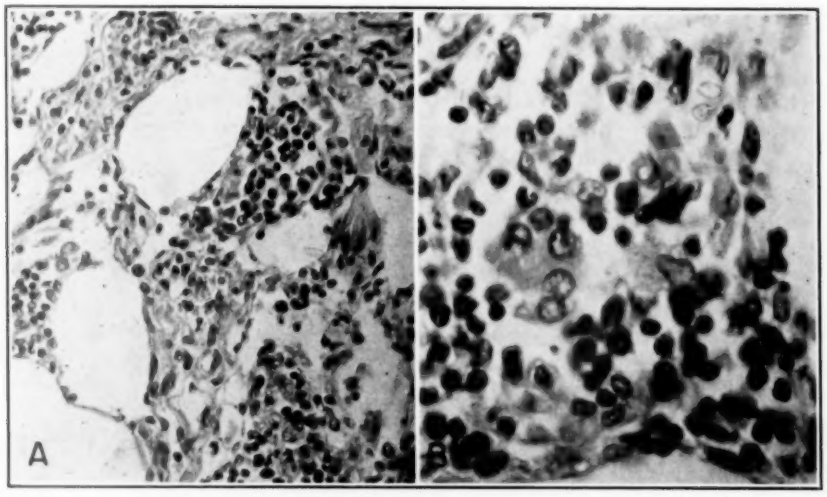

FIG. 2.—A A mesenteric lymph node showing the granulomatous reaction and occasional giant cell at the periphery of the fat filled spaces. (X 300)
B Same, showing a large space surrounded by numbers of the typical macrophages. (X 1000)

100 to 102° F., with irregular swings to 104°. She developed increasing ascites.

An exploratory laparotomy was performed. A large amount of milky fluid was removed. The small intestine was dilated, thickened, and showed a subserosal accumulation of a milky substance. The mesenteric nodes were large and rubbery. This was interpreted as representing Whipple's disease.

She continued a downhill course, losing weight and developing subcutaneous abscesses. Paracenteses were performed. There was increasing cardiac insufficiency and she developed a gallop rhythm and a pericardial friction rub. She expired 64 days after admission, 144 days after the onset of symptoms. (Diarrhea was present briefly, only upon one occasion, during her illness.)

NECROPSY. The peritoneal surfaces were lusterless but there was no exudate. The pleurae were normal. The pericardium showed a friable gray membranous exudate. The heart was grossly normal. The lungs showed extensive areas of irregular peribronchial consolidation. The small bowel was generally thickened and the jejunum was gray-white while the ileum was of a yellow-orange color. The gray and yellow colors of the gut were the result of subserosal accumulations. A network of lymphatic channels was well outlined, increasing in size in the mesentery. Cutting the mesentery permitted the milky fluid to exude but left visible channels suggesting thickening of their walls. The lymph nodes were prominent but not greatly enlarged. They were pale, firm, gray in color. The thoracic duct and cisterna were normal. No other gross changes were noted.

Microscopic Examination. There was an irregular generalized thickening of the alveolar walls of the lungs with many large mononuclear cells.

The heart showed a subepicardial accumulation of mononuclear cells, with fibrinous exudate over the epicardium. The muscle fibers were not greatly altered (Fig 3B).

The intestinal mucosa was intact. There was an increase of lymphocytes in the lamina propria. The villi showed foamy phagocytes and rarely a clear space at the distal end. The submucosa was greatly thickened due to an accumulation of mononuclear phagocytes having clear or foamy cytoplasm; they were in the tissue spaces and also lined the thin-walled lymphatics. The fat-filled phagocytes extended through the muscularis. Numerous multinuclear giant cells were present either free or collected about the lymphatic spaces. Sections through the mesentery showed similar changes (Fig. 3A).

The mesenteric lymph nodes showed dilated lymphatic channels. With fat stains it was shown that they were filled with fat which was free as well as in the phagocytes. They were grossly distorted with reduced cellular detail and an increase in abnormal phagocytic cells, some of which were relatively undifferentiated. No eosinophils were present.

The liver showed periportal accumulations of vacuolated cells. In the pancreas there were accumulations of cells similar to those seen in the gut, but there was no free or phagocytosed fat. The kidneys showed dilation of the tubules; in the glomeruli there was focal thickening of the basement membrane and sometimes of a part or all of the tuft (Fig. 3C). There were no arterial lesions.

The anatomical diagnoses were: 1) disseminated lupus erythematosus, 2) intestinal lipodystrophy of Whipple, 3) fibrinous pericarditis, 4) interstitial pneumonia, 5) acute glomerulitis.

Note: The fat in the jejunum was found to be similar to that in the ileum but contained, however, considerably more carotene.

CASE 3. An 11-year old white boy was admitted to Vanderbilt University Hospital on June 9, 1945, because of abdominal distention and diarrhea. In addition there had been occasional vomiting. These disturbances had been present intermittently over the preceding year. He had lost weight and there had been some generalized edema. There had been no associated fever or arthralgia.

Past History. In October, 1938, he had been studied in the hospital for a complaint of unilateral swelling of his face which dated from birth. Also he had always had a rough scaly skin, more marked in the winter, and for several months he had had brief periods of inability to use his right arm and leg. The examination revealed presumably cerebral gliosis and a mild ichthyosis; a congenital malformation of the lymphatics of the face was presumed to account for the unilateral facial swelling. Somewhat later he began to have grand mal seizures for which he had to take sedatives, phenobarbital and dilantin.

Physical Examination. The height was 51 in., weight 59½ lb., and blood pressure 98/64. He was poorly nourished and developed; the skin was dry and scaly. The lungs were clear and the heart normal. The abdomen was distended and doughy and shifting dullness could be elicited; there was no muscle spasm and no abnormal masses were palpated. Otherwise, the examination was not remarkable.

Gastro-intestinal examination showed segmentation of the barium in the small gut. Otherwise, Roentgen studies were negative.

Laboratory Findings. Renal and liver function tests were normal. Blood studies showed: RBC 5.6 million, Hgb. 15 gm., WBC 10,000 with 2% eosinophils, otherwise the differential was normal. Serum calcium was 8.4 and phosphorus 5.0 mg., alkaline phosphatase 9.4 Bodansky units, serum protein 4.32 gm. (albumin 2.23 and globulin 1.09 gm.) Vitamin A absorption test: fasting 223, 5 hr. 96 and 9 hr. 173 I.U. Glucose tolerance test: fasting 133, 14 min. 167, 30 min. 250, 1 hr. 210, 2 hr. 171, 3 hr. 141 mg. Stool nitrogen was 177 gm. per 24 hours. Stools were negative for parasites either bacterial or protozoal.

A tentative diagnosis of Whipple's disease was entertained to explain the failure in protein metabolism and the failure of intestinal absorption. A laparotomy was performed to evaluate this hypothesis.

The peritoneal cavity was filled with a milky fluid; (protein 66 mg. per 100 cc., fat 1.63 gm., and cholesterol 33 mg.) The liver and spleen were normal. The gut was dilated, thickened, and of a grayish-pink color, with many small yellow flecks and dilated lacteals within the walls; the latter extended into the mesentery. The lymph nodes at the base of the mesentery were enlarged, 1 to 2 cm. in size, discrete, and rubbery in consistency.

Biopsy of the gut wall, excepting the mucosa, and of the lymph nodes showed accumulations of large mononuclear phagocytes with foamy or clear cytoplasm. There were also small fat accumulations similar to those seen in the lymph nodes in the subserosa and in other parts of the gut (Fig. 4).

These studies seemed to substantiate the diagnosis of Whipple's disease.

Course. He was put on a diet high in protein (6 gm. per kilo per day), high in carbohydrate, and low in fat. On this regimen he has been able to remain free of diarrhea and ascites, though he consistently has total protein values of 3 to 4.33 gm., with a 5:3 A/G ratio.

On 4 occasions he has been readmitted to the hospital to observe the effects of albumin administration, the effect of testosterone, the effect of fat-dispersing agents such as Tween 80, and finally, the effect of cortisone.

On one of the admissions the following balance studies were carried out (Table I):

None of the efforts at therapy have yielded any significant and lasting effect upon the illness. The administration of large amounts of albumin did invariably raise the total proteins and allow him to become edema free, a feature of his illness never apparent except after such a diuresis.

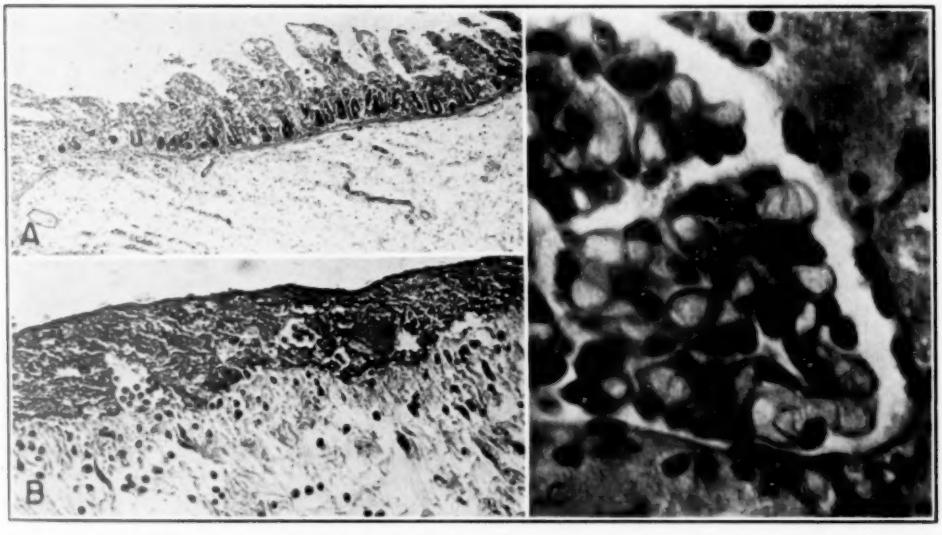

FIG. 3.—A The lamina propria (Case 2) showing the same reaction as in Fig. 1-A. Sudan III stain showed neutral fat in the spaces in the lamina propria. (X 60)

B The epicardium in Case 2 showing the fibrinous exudate. The cellular exudate is predominantly mononuclear. (X 300)

C Portion of a glomerulous from Case 2 showing typical "wire-loop" lesions. (X1200)

On the diet prescribed he has been able to grow and develop in a fairly normal manner.

CASE 4. A 47-year old white farmer was admitted to the Vanderbilt University Hospital on Oct. 18, 1947, because of breathlessness, abdominal pain, and diarrhea. He began to suffer from very severe, sharp, sudden attacks of cramping abdominal pain 4 to 5 years before admission. They were referred to the upper abdomen bilaterally, were more severe on the right side, and lasted about 20 minutes. At this time he had pain and swelling of many of his joints, though there was no redness or heat. A year after the onset a diagnosis of cholecystitis was made. Cholecystectomy and appendectomy were carried out. The gallbladder was "full of pus". He improved for 6 months. During the following 3 years he had gradual weight loss, increasing malaise, weakness, cramping lower abdominal pain, and some sharp right-sided subcostal pain. One year before admission he began to have bouts of hard shaking chills and fever followed by drenching sweats. These symptoms improved after a course of penicillin. In the few months before admission there was diarrhea, 5 to 8 stools daily; twice there was gross bleeding. Recently food passed through unchanged and the bowels moved so promptly after eating, that he was forced to leave the table at times. Nausea and sometimes vomiting appeared within an hour after meals. For two months before admission there had been dyspnea, orthopnea, swelling of the ankles, and increasing size of the abdomen. "Red spots" had appeared on the legs and thighs. His usual weight had been 165 pounds; 2 months before admission it was 135 and upon admission, 128 pounds.

FIG. 4.—A mesenteric lymph node from Case 3 showing persistence of some relatively normal lymphoid tissue and replacement of the remainder by fibrous connective tissue and fat-filled, endothelial-lined spaces. (X 30)

Past History. Up to 10 years before admission the patient had drunk whiskey in large quantities. He had had pleurisy and gonorrhea.

Physical Examination. The patient was dyspneic and poorly nourished. The skin was pale or sallow and dry and loose. A petechial rash was present on the legs and the right arm. There were a few enlarged lymph nodes in the cervical chains. There was moderate arteriosclerosis of the arterioles of the optic fundi. The heart was not enlarged; the pulmonic second sound was accentuated. The blood pressure was 90/60. The abdomen was large with evidence of ascites. The liver edge was palpable two fingerbreadths below the costal margin. A "doughy" sensation was present upon palpation of the abdomen. One observer felt a mass in the left upper quadrant.

Roentgen-ray Examinations. After the removal of 40 cc. of serosanguineous fluid by abdominal paracentesis, air was injected. With the aid of pneumoperitoneum in addition to the fluid, the liver and spleen were shown to be moderately enlarged but smooth, and adhesions were shown in the left upper abdomen. A chest film was negative. Gastrointestinal series showed no esophageal varices, a coarse mucosal pattern, once a duodenal ulcer was suspected, and once barium was delayed in passing the second and third portions of the duodenum. Carcinoma of the pancreas was suspected. A barium enema and retrograde pyelograms revealed no abnormality.

An electrocardiogram showed a low voltage QRS complex.

leathery; these characteristics gradually disappeared toward the terminal ileum which was quite normal. In the retroperitoneal tissues, inferior to the origin of the superior mesenteric artery, was a globular mass 12 by 15 cm. in diameter. In the jejunal mesentery were found several large nodes up to 4 cm. in diameter. One was removed and upon cutting it, it was thought to represent Hodgkin's disease. The liver and spleen were normal.

Microscopic study of the lymph node removed at operation showed a fibrous capsule. All the lymphoid tissue had been replaced by dilated lymph spaces lined by a single layer of endothelium and containing a pale eosinophilic amorphous substance. Between the large dilated lymph spaces were small amounts of lymphoid tissue and large mono-

TABLE I—DIET BALANCE STUDIES IN CASE 3

	Total Intake	*Urinary Excretion*	*Stool Excretion*
Protein	1037 gm.	449.8 gm. protein Eq.	119.4 gm. (11.5%)
Fat	340 gm.		66.0 gm. (19.4%)
Dried Stool fat was 38.6%			

(Normals should be: Stool protein less than 1 gm., ± .6 gm./day.
Stool fat ± 3 –4 gm./day.)

These figures illustrate the failure of protein and fat absorption.

Laboratory Findings. Urinalysis showed sp. gr. to 1.025, and occasional white and red blood cells were constantly present. Blood studies: RBC 4 to 4.8 million, Hgb. 10.5 to 11.5 gm., P.C.V .35, MCV 77 cuμ, MCHC 35%, sedimentation rate 21 mm., WBC 8000 to 14,000, with normal differentials. The blood Wassermann and Kahn tests were postive once and negative once. Blood chemical tests: NPN 30, cholesterol 115, and blood sugar 89 mg.; vitamin C zero (3 times); serum amylase 45. Oral glucose tolerance test: 1 hr. 119, 2 hr. 108, and 3 hr. 101 mg.; serum protein 4.63 gm. (albumin 2.60 and globulin 2.03 gm.). Gastric analysis showed free hydrochloric acid after histamine. Coagulation time was 11 min., bleeding time 3 min., prothrombin time 16.5 seconds (control 10 seconds). The results of liver function tests were within normal limits. Ascitic fluid showed: protein 3.02 gm. per 100 cc., RBC 40,000, WBC 8200, a differential count of neutrophils 74%, lymphocytes 20%, monocytes 6%; organisms were not demonstrated by culture or guinea pig inoculation. Occult blood was present in the stool on 3 occasions. The venous pressure was 28 cm. of water; the circulation time was 21 seconds, arm to tongue.

An *exploratory laparotomy* was done on Nov. 11, 1947. Water-clear ascitic fluid was found. The jejunum was large, thick, and nuclear phagocytes having a foamy cytoplasm: some of these cells contained one large globule of fat. There were many plasma cells, eosinophils, a few polymorphonuclear cells, and giant cells, as well as an increase in fibroblasts. Fat was shown with Sudan III.

Course. The patient was afebrile but continued to lose weight, 128 to 117 lb. He was discharged Dec. 6.

SECOND ADMISSION. He was readmitted on Jan. 10, 1948, for Roentgen-ray therapy. Diarrhea, nausea, and vague abdominal discomfort had persisted. The abdomen felt "doughy"; the liver was palpable. The blood pressure was 100/60. Weight was 120 lb. The electrocardiogram again showed low voltage.

Laboratory Findings. There were no significant changes from the previous study except in the vitamin A absorption test, which showed fasting 62, 4 hr. 107, and 8 hr. 102 international units. Vitamin C absorption test showed fasting 0, 4 hr. 0. Stools were positive for occult blood 3 times.

Course. He was given 1600 R to the upper abdomen posteriorly and 1800 R anteriorly and was discharged Feb. 2, 1948.

A letter from the family physician indicates that the nausea and diarrhea persisted and that the patient died of "terminal pneumonia" about two weeks after discharge.

Clinical Picture. Of the collected cases, 23 were in men, 2 in women, and in 1 the sex was not given. One was as old as 74 years, and 2 of our patients were 11 and 13 years, respectively (Table 2).

TABLE 2.—SEX AND AGE IN 26 CASES OF INTESTINAL LIPODYSTROPHY

Sex	
Males	23
Females	2
Unknown	1
Age	
10–19 years	2
20–29	1
30–39	5
40–49	8
50–59	6
60+	3
Unknown	1

SYMPTOMATOLOGY. The onset is insidious in most instances. This is especially true if one dates the onset to some of the symptoms unrelated to the gastro-intestinal tract. The progression does not follow any regular pattern. Table 3 presents the symptoms mentioned and their frequency, as recorded. Obviously in some cases one symptom appeared first and in others another.

If arthritis and arthralgia are admittedly part of this disease, as we believe them to be, they commonly mark the onset. In the 17 instances in which a history of arthritis was recorded, all but one had had recurrent bouts of pain in the joints for several years and even up to 10, 13, and 15 years, and the joint pains often antedated the abdominal or constitutional symptoms. In about a third of cases they arose at the time of the other manifestations. One had had joint and other symptoms for only 6 months. The joint manifestations were swelling and stiffness, and in a few cases redness and heat followed by a residual picture like that of rheumatoid arthritis. One patient gave a history of subcutaneous periarticular nodules during acute attacks. Bouts of "chills and fever" were reported by several patients during the periods of arthritis or arthralgia.

The period during which there were symptoms referable to the gastro-intestinal tract varied from 2 months to 4½ years (Table 3). Most of the patients had had such symptoms for 1 to 3 years before they were studied. Death occurred commonly within a matter of weeks or months subsequent to the first hospital admission.

TABLE 3.—SYMPTOMATOLOGY AND THEIR DURATION (EXCLUSIVE OF ARTHRITIS) IN 26 CASES OF LIPODYSTROPHY

Duration to death		*Symptomatology*	
1–11 months	7	Arthritis	17
12–23 months	6	Weight loss	21
24–35 months	3	Weakness	15
36+ months	7	Anorexia	12
Unknown	2	Abdominal distention	21
Alive	1	Abdominal pain	18
		Vomiting	9
		Diarrhea	23
		Constipation	1
		Diarrhea-constipation	5
		Blood (gross) in stools	4
		Dyspnea	7
		Edema of ankles	7

Abdominal distention and, less commonly, upper abdominal pain, were frequent presenting complaints. Though a few were constipated at first and then developed diarrhea, almost all of the patients suffered from diarrhea some weeks or months after the onset of the initial abdominal symptoms. In a few instances it appeared late in the clinical course and never was a prominent symptom. In other cases it alternated with bouts of constipation. When the number of stools was listed (in 6 cases only) they varied from 3 to 8 per day, being described as gray and watery in 2, in 1 as greasy, in 1 as mucoid, and in 2 as white, in 1 as soft, in the other

as "creamy". Gross blood was mentioned in 4 cases. Vomiting occurred at times in 9 patients, usually after eating. Anorexia was reported in 11 cases and a good appetite in 3.

Weakness and ease of fatigue were also prominent symptoms and several times were the initial subjective abnormality. Weight loss went hand in hand with weakness and at times was extreme. In several cases the eventual weight loss was 25 to 33 per cent of the original weight, and in 2 it was 50%. This occurred not infrequently within a matter of months. Twenty patients reported weight loss.

Breathlessness and palpitation were part of the general debility and probably were also in part an expression of the accompanying anemia.

The frequency of ankle edema may be explained by the loss of tissue pressure due to the rapid, and at times severe, weight loss, as well as by the hypoproteinemia. Of interest is a patient who 4 years before admission had had suddenly blurred vision which led to blindness within a few days. It was diagnosed as retrobulbar neuritis, and several years later as optic atrophy. Our patient (Case 2) with disseminated lupus had visual symptoms.

The *physical findings* which are listed in Table 4 were few but quite consistent. The evidence of weight loss was commonly apparent and extreme emaciation was present in a number of instances. Pallor was described not infrequently.

Pigmentation of the skin, especially of the exposed areas, was noted in 10 instances. Several authors took the trouble to point out that the pigmentation did not involve the axillae, genitalia, or "pressure areas" of the extremities, and that no pigmentation was discernable in the buccal mucosa. In several instances the pigmentation suggested Addison's disease and required differentiation from this condition. Erythema nodosum, urticaria, petechiae, and "red spots" were found in 1 patient each.

Of 16 patients in whom the blood pressure was reported, 15 had systolic pressures of 100 mm. of mercury or less. Commonly the pressure was about a 90/60.

Hypothermia, temperature levels of 95.5 to 97° F., was present in 3 cases. A low-grade fever was present in 2 patients while under observation, and in our second case there was moderate fever.

A mass described as being firm, hard, and nodular, with more or less abdominal fullness, was found in 6 instances. The abdomen gave a sensation of "doughiness" in 4 patients. Ascites, diagnosed clinically at operation or at autopsy, was present in 9 instances, being "milky" in 4. The spleen was felt in several patients.

One patient was noted as showing the joint changes of rheumatoid arthritis. Generalized lymphadenopathy is mentioned frequently.

A pericardial friction rub was heard in 2 patients.

Roentgen-ray Findings. Examination of the chest showed nothing remarkable in 5 patients (Table 4). In Case 2 of this report, irregular densities were reported in the lower lobes.

Barium enema revealed no abnormality in 6 instances in which this was done. A gastro-intestinal series was carried out in 16 cases. In one instance there was "spasm" or obstruction of the splenic flexure of the colon with a delay of barium at this point for 36 hours. Two patients had evidence of abnormal motility in the bowel as shown by "laking" or "puddling" of barium in the jejunum and upper ileum. One had delay in the movement of barium in the second and third portions of the duodenum. Five were reported as showing an increased rate of passage of the barium through the small bowel. One

showed an extrinsic pressure deformity of the stomach. Three showed a "coarse duodenal and jejunal mucosal pattern". Four patients had no gastrointestinal abnormality demonstrable by the Roentgen-ray.

Laboratory Findings. As might be surmised, the laboratory observations tabulated have been of a great variety and of scattered frequency. Very few studies have been carried out consistently, as is to be expected in 26 isolated cases reported over a period of 42 years. These findings are summarized in Table 5.

The only consistently reported laboratory studies were the hemoglobin determination and the red and white cell counts. A hypochromic or microcytic anemia commonly accompanies intestinal lipodystrophy when it has reached the grade requiring hospitalization. (It is noteworthy that macrocytic anemia was reported in only 1 case, a point of assistance in the differentiation of the disease from sprue.) Many of the white blood counts were within normal limits. Leukocytosis of from 10,000 to 19,000 per c.mm. occurred in 6 patients. Two higher counts, 24,000 and 40,000, were recorded; in both instances the predominating cell on the differential count was the lymphocyte[7,20]. A diagnosis of leukemia was made in the second of these cases and treatment was instituted with radioactive phosphorus. Later splenectomy was done. A differential

TABLE 4.—FINDINGS UPON PHYSICAL AND ROENTGEN-RAY EXAMINATION IN 26 CASES OF INTESTINAL LIPODYSTROPHY

Physical examination		*Roentgen-ray examination*	
Emaciation	16	Chest	
Hypotension	16	Negative	5
Abdominal mass	6	"Patchy densities"	1
Ascites (by signs, at operation, or necrospy)	9	Barium enema (negative)	6
Cutaneous Findings:		Gastrointestinal	
Pigmentation	10	Negative	4
Purpura	2	Increased motility	5
Erythema nodosum	1	Decreased motility	2
Urticaria	1	Coarse mucosal pattern	3
Lupus	1	Gastric deformity (extrinsic)	1
		Splenic flexure obstruction	1

TABLE 5.—LABORATORY FINDINGS IN 26 CASES OF INTESTINAL LIPODYSTROPHY

Hgb. decreased	22	Serum proteins	
RBC decreased	22	Total—below 6 gm.	9
RBC normal	4	Total—above 6 gm.	4
WBC normal	17	Albumin—below 4 gm.	11
WBC leukocytosis	7	Globulin 2.5 gm. or more	8
Differential normal	13	Glucose tolerance test	
Lymphocytosis	3	Normal	4
Eosinophilia	4	"Flat"	7
Sedimentation rate		Vitamin A absorption test	
Normal	5	"Flat"	4
Elevated	4	Stools	
Cholesterol, "Normal" 71, 76, 115, 143 mg. (in 5 cases)		Occult blood	7
		Fat (dry weight) 26, 38, 39, 44, 56, 59% (in 6 cases)	

count was reported in one-half of the cases. Except as just indicated, these were within normal limits. An eosinophilia of from 5 to 13% was reported in 3 cases. The sedimentation rate was elevated in 4 of the 9 cases in which it was reported.

The urine rarely showed any abnormality. Two of our patients had an occasional red cell in the sediment. One of our group (Case 2) had slight albuminuria, as did one other patient.

Achlorhydria was present in 7 instances and acid was present in 2. Some had no acid, even after histamine. This is not significant in view of the age group encompassed in these patients. No comment was made in the remainder of the cases.

Serum proteins have shown a depression in 9 of 12 patients so examined. There was no azotemia in 9 patients, and it was present in one. The blood cholesterol was "normal", 71, 76, 115 and 143 mg. in 5 patients, respectively. The few serum calcium and phosphorus examinations showed normal values. Scattered liver function tests revealed no abnormalities. Normal serum sodium and chloride values were reported in 4 instances. Oral glucose tolerance tests showed flat curves in 7 and a normal curve in 4 patients. Vitamin A tolerance curves were flat in 4. Serologic tests for syphilis were positive or doubtful in 3.

Stools were reported as showing occult blood in 7 instances. Studies for stool fat were carried out in 6 cases. The percentages of dried fat stool weight were 26, 38, 39, 44, 56, and 59, respectively.

Many of the case studies are quite incomplete as to laboratory studies for two reasons. In many instances the disease was not recognized or suspected during life, and secondly some of the pertinent laboratory studies have been available only in recent years.

PATHOLOGICAL ANATOMY. The significant gross lesions in Whipple's[25] case were polyserositis, endocarditis, a small intestine thickened generally but particularly the mucosa which was velvety, minute yellowish accumulations just beneath the mucosa, enlarged mesenteric glands with disturbed architecture and cystlike accumulations of fat. Histologically there were enlargement of the intestinal villi and thickening of the submucosa. The epithelium of the mucosa was normal and the interglandular spaces contained the usual numbers of lymphocytes, plasma cells, and eosinophils, but was crowded with large mononuclear cells, some with a pink protoplasm and others with an abundant foamy protoplasm. Lymph nodes were enlarged with small and large accumulations of fat and fatty acid, intra- and extracellularly. Larger deposits occupied spaces lined with endothelium suggesting dilated lymph channels, often outlined with polynuclear, giant, or "polyblastic" mononuclear.

While it is certain that one does not have to have precisely these features to establish a diagnosis of intestinal lipodystrophy, the lesions in the intestine and lymph nodes should be entirely characteristic when they must stand by themselves.

Table 6 summarizes the gross findings, and Table 7, the microscopic findings described in the gut and lymph nodes in the 23 patients coming to necropsy and in 3 instances in which the diagnosis was established at laparotomy and by biopsies. The table also includes the vascular lesions described in the mesentery and kidneys.

Hendrix, Black-Schaffer, Withers, and Handler[11] in their recent study emphasize two common pathologic findings and the absence of a third finding as being characteristic of Whipple's disease. These are: the presence of a nonsudanophilic macro-

phagocytosis in the lamina propria of the intestine, glandular lipogranulomatosis, and the absence of anatomic evidence of chylous obstruction.

We cannot agree with them that dilatation of the lacteals peripheral to the lymph nodes is a significant differential point. If one uses this criterion in a rigid manner, it would exclude from consideration all our cases and would also exclude Whipple's case and that of Sailer and McGann[23], cases which Hendrix and his associates have accepted as typical. In this connection it is of interest that our third patient had chylous ascites when no attempts at dietary control were exercised but that he has not shown ascites in a demonstrable amount in the subsequent 4 years, although his serum proteins have not been above a level of 4 gm. The question of whether or not chylous fluid will accumulate in the peritoneum is probably related to the degree of obstruction in the lymph nodes from the lipogranulomatosis and secondary obstruction of the mesenteric and subserosal lacteals; it may also be secondary to the serositis, as in Case 2. This patient with marked recurring chylous ascites showed no evidence at postmortem examination of obstruction of the cistern or the thoracic duct.

TABLE 6.—GROSS ANATOMICAL FINDINGS AT NECROPSY IN 23 CASES OF INTESTINAL LIPODYSTROPHY

Pericarditis		14	
Adhesive	6		
Active	8		
Pleuritis		10	
Adhesive	2		
Active	8		
Peritonitis		7	
Disease of serous-lined cavities—not mentioned		4	
Valvular Disease		9	
Vegetations	7		
Inactive disease	2		
Mesenteric Nodes, enlarged		22	
Abnormality of Gut		21	

TABLE 7.—HISTOLOGIC FINDINGS IN INTESTINAL LIPODYSTROPHY

Intestine	
Invasion lamina propria by vacuolated macrophages	17
Dilated spaces—fat stain positive	13
Lipogranulomatosis of mesenteric nodes	
(Giant cells, foam cells, endothelial lined spaces—absence or distortion of normal lymphoid structure)	
Spaces—positive with fat stain	21
Macrophages—positive with fat stain	14
Vascular lesions	
In mesentery	2
Glomerular "wire-loop"	1
Arteriolosclerosis (kidney)	3
Intestine— 1 case —subserosa invaded by foam macrophages	
Mesenteric nodes—3 cases—pathologic findings as above	

Whipple's intestinal lipodystrophy, in our opinion, is characterized primarily from a clinical viewpoint by the occurrence of severe nutritional failure occurring in rheumatic subjects, or perhaps as an isolated manifestation. These patients have abnormal absorption of fat, and possibly other foods, with a concommitant phagocytosis of fat and other metabolites[3] with their

retention in the lamina propria of the intestine and in the regional mesenteric nodes. There may or may not be associated blockage of the lacteals. The exact pathogenesis of these lesions is not apparent from the studies to date.

The 30-odd cases which have been reported or considered as examples of Whipple's intestinal lipodystrophy have not presented a uniform picture from either the clinical or pathological viewpoint, and as the picture is better clarified by the multiplication of cases it seems possible to make some differentiations.

There are a number of diseases which may give clinical pictures like that seen in Whipple's disease but which can readily be differentiated on the basis of pathological examination. In this group one may list tabes mesentericus in which there is obstruction of lymphatics due to tuberculosis of the mesenteric glands, with or without associated tuberculous ulceration of the intestinal tract. One may also find obstruction due to lymphomatous processes, such as Hodgkin's disease. Cases of sprue would be readily differentiated pathologically by their failure to show lipogranulomatosis of the mesenteric nodes and clinically by the common association with macrocytic anemia. Nutritional failure secondary to pancreatic insufficiency would readily be separated by the examination of aspirated duodenal fluid. One should also list chyladenectasis which, though usually producing a picture clinically unlike Whipple's disease, may at times be confused with it. Hill's[12] case was, for example, listed as chyladenectasis.

On the basis of the clinical and pathological characteristics noted above, it seems possible to separate 8 cases from the group classically representative of Whipple's intestinal lipodystrophy.

The first of these are the cases of Blumgart[4]. His first case showed neither the intestinal nor the lymph node lesions. The second case, while it could possibly be an instance of Whipple's disease, is not described in complete enough detail for acceptance, particularly as related to the description of the lymph node lesions. The third case is probably either one of tuberculosis or histoplasmosis.

The case of Pearse[18] might be an example of Whipple's disease, but the only pathological studies of lesions are more consistent with chyladenectasis. No microscopic studies of the gut or lymph nodes were made.

Boeck's[5] case report is too fragmentary for consideration.

In the cases of Pemberton[19] and his associates, there was no evidence of disturbed absorption, but all 3 seemed to be primarily related to some inflammatory or neoplastic obstruction in the lymph nodes. The absence of the typical pathological picture in the lymph nodes and the lack of examination of the small intestine make it impossible to include these cases as examples of Whipple's disease.

The cases of Reinhart and Wilson[20] and of Fitzgerald and Kinny[7], while not entirely typical, are, so far as the intestinal lesions are concerned, so similar to others in the group that the presence of lacteal dilatation is not deemed sufficient to exclude them from the group. The findings from these cases have been included in our tabulations, but those of the other 8 cases are not considered.

The case of Rosen's[21] was retained even though the examination did not, in the presence of chylous ascites, exclude obstruction to the thoracic duct. Pathologically, it is otherwise entirely acceptable.

Discussion. There have been numerous theories concerning the pathogenesis of Whipple's disease but they have little to recommend their serious

consideration. Among them one may mention Jarcho's[13] theory that the reaction results from dilatation of the lymphatics secondary to obstruction in the node either congenital or from some other unexplained cause. Sailer and McGann[23] postulate the reaction as resulting from fat necrosis with lipolytic ferments serving to produce the irritation and lipogranulomatosis. Hass[10] has postulated that the fatty acids with high melting point might serve as a source of irritation to produce the inflammatory reaction. Reinhart and Wilson[20] thought the reaction might be secondary to an abnormal excretion of fat into the intestine with increased resorption. Stryker's studies on the changes in the intestine and lymph nodes following prolonged administration of liquid petrolatum are cited by Black-Schaffer[11] as being highly suggestive. However, it is impossible in most cases to associate abnormal fat ingestion with the pathogenesis of the disease, particularly since diarrhea was in many instances the first symptom. Newman and Pope[16] suggest, as does Jarcho, that the fundamental lesion is an obstruction in the lymph node, due to some chronic inflammatory process. None of these theories except that of Black-Schaffer and his associates takes into account the association of arthritis, serositis, and endocarditis so commonly encountered. They suggest that the disease may be a sequel to or the result of an unidentified systemic illness characterized by inflammation of the serous membranes, joints, and pericardium. They also postulate that the lesions in the gut and the lymph nodes may be the result of a phagotactic substance which promotes or induces the phagocytosis of an unidentified substance in the lamina propria and of fat in the lymph nodes. Subsequently they[3] have identified this phagotactic substance as a glycoprotein.

Fleischmann[8] in his report emphasized the vascular changes and assumed that the whole disturbance was secondary to circulatory disturbances. Korsch[15] also noted vascular changes in his patient but felt that they were not of primary significance.

It is our belief that Whipple's disease is another manifestation of the "rheumatic state" or generalized collagen disease.* The association in these patients of manifestations common to this state is striking and occurs with a frequency scarcely to be attributed to coincidence.

In this connection it seems significant to us that our second case was a fairly typical example of generalized disseminated lupus and that our first and fourth cases, adult patients, had had rheumatoid arthritis as a part of the clinical picture.

The third case to date has shown no other manifestations of the rheumatic state, but it is not uncommon to see for long periods of time an isolated single manifestation of the "rheumatic state" in a patient. (It is, of course, possible that the lesion in this patient differs from the classical group and is indeed a congenital anomaly of the lymphatics. In favor of this hypothesis is the fact that he had a disturbance of the facial lymphatics, but against it is the point that he was free of symptoms attributable to the intestinal lesion until the age of 9 years.)

Though incontrovertible proof from a pathologic viewpoint is lacking, we feel that a strong case can be made for the inclusion of intestinal lipodystrophy in the great group of "rheumatic" or collagen diseases. Early in the evaluation of any rare clinical entity, before accumulated experience has placed its pathogenesis on a firm,

* This concept was first raised in discussions of Case 2 with Dr. James R. Dawson.

basis, circumstantial evidence only may be marshalled. We have presented the findings from the reported instances of this rare disease from a clinical standpoint in order to present the over-all clinical syndrome.

A brief analysis of these findings will, we believe, allow us to hypothesize that Whipple's disease belongs in the same group as lupus erythematosus disseminatus, periarteritis nodosa, rheumatoid arthritis, rheumatic fever, scleroderma, dermatomyositis, serum sickness, and possibly others now viewed as examples of collagen disease or the "rheumatic state."

In two-thirds of the patients, the manifestations of generalized systemic disease outside of the gastro-intestinal tract antedated the localizing abdominal symptoms by months and even years. The stage of recurrent arthritis, lymphadenopathy, malaise, weakness, weight loss, chills and fever observed in these cases of Whipple's disease are symptoms which are common manifestations of the early phases of disseminated lupus erythematosus or of rheumatoid arthritis. The occurrence of arthritis in 65% of the cases seems more than a simple coincidence. The frequent occurrence of otherwise unexplainable generalized lymphadenopathy is also of considerable importance and significance, we believe, in this respect. The association of generalized pigmentation in a degree sufficient to require consideration of Addison's disease in one-third or more of the cases may be no more than the manifestation of the severe malnutrition in these patients, but even in this respect it suggests a systemic disease of greater magnitude than simple failure of nutrition due to blockage of the intestinal absorption. The concomitant finding of erythema nodosum in one patient and lupus erythematosus in another patient is also of general interest and significance.

The anatomic findings at necropsy serve even better as a basis for considering intestinal lipodystrophy to be a disease of general involvement (Table 7). An incidence of serositis in 82.6% of the 23 cases seen at autopsy is a very striking association. Among the 19 instances of inflammation of serous-lined cavities, there were 14 with pericarditis, or 60% of the total cases coming to necropsy; 10 (43%) had pleuritis; and 7 (30%) had peritonitis. In addition to these findings there is the fact that 7 (30%) of the patients had vegetative endocarditis which was active at the time of examination and an additional 2 (9%) showed healed valvular endocarditis. Furthermore, Jarcho's[13] case had Aschoff bodies in the myocardium.

Korsch[15] and Fleischmann[8] described inflammatory vascular lesions of the mesentery in their patients, and Fitzgerald and Kinney[7] and Jones and Paulley[14] reported vascular lesions in the optic fundi in each of their cases. Case 2 in our group showed extensive retinal exudate. Case 4 in our study showed moderate arteriolosclerosis. The cases of Glynn and Rosenheim[9], Reinhart and Wilson[20], and of Hill[12] showed arteriolosclerosis demonstrable in the kidneys. Case 2 of our series showed the typical wire-loop glomerulitis of disseminated lupus erythematosus.

These associated anatomical findings, distinct and apart from the lesions in the intestines and mesenteric lymph nodes, together with the common occurrence of arthritis and other symptoms and findings often seen in other examples of collagen disease seem to us to justify the assumption that Whipple's intestinal lipodystrophy is another manifestation of that reaction group. We believe that these associations might have been reported more commonly if some findings had not been ignored as being unrelated.

It seems altogether probable to us that a more careful search, of the mesentery, for example, directed toward lesions associated with the rheumatic state will result in further clarification of this remarkable association.

Summary. 1. Four cases of Whipple's intestinal lipodystrophy from the files of the Medical and Pediatric Services, Vanderbilt University Hospital, have been added to the case reports of Whipple's intestinal lipodystrophy.

2. The reported cases of Whipple's disease have been analyzed to present an over-all clinical picture of the disease as represented by a total of 26 acceptable cases.

3. The various ideas concerning the pathogenesis of Whipple's disease have been reviewed.

4. The thesis is advanced that Whipple's disease is another manifestation of the "rheumatic state."

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AN EVALUATION OF ARTANE AND TOLSEROL IN THE TREATMENT OF SPASTIC DISORDERS

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In their original published reports on the pharmacological properties of Myanesin† (α, β, dihydroxy-γ (2-methyl-phenoxy) propane), Berger and Bradley[2] stated that small doses selectively depressed reflex excitability of the spinal cord and larger doses produced an "ascending depressant action on the central nervous system". They postulated its usefulness in obtaining muscular relaxation during light anesthesia. Later, Berger[1] added: "It should prove useful in the treatment of spastic paralysis, hypertonic states and tremors". Spasticity is due to the exaggeration of the normal facilitatory stimuli on the lower motor neurones with or without a release from inhibitory influences[13]. In their experimental studies with cats Henneman, Kaplan and Unna[11] found Tolserol would abolish facilitation and inhibition of stretch reflexes originating from various levels of the central nervous system. The site of this depressant action was determined to be on the internuncial neurones in the spinal grey matter and on both the facilitatory and inhibitory centers in the brain. Therefore, they concluded that all types of spasticity should respond to treatment with this drug.

The results of clinical trials with Tolserol have been contradictory and disappointing, except in the acute muscle spasms of the rheumatic disorders, the "acute low back", and in the discogenic syndromes[15,17]. Mallinson[14], Wilson[19], and Davison[6] confirmed its value in obtaining adequate abdominal relaxation during anesthesia; but these results have been challenged by Gray[9] and Woolmer[20]. Griffith and Cullen[10] believe it produces muscle relaxation only in an anesthetized patient.

Similarly, there have been contradictory reports concerning the effectiveness and optimum method of administration of Tolserol in the spastic disorders. Henneman and Scherrer[12] were able to relieve all types of experimental spasticity in cats. In human subjects, Schlesinger, Drew and Wood[16] diminished the overactivity of the stretch reflex with Tolserol intravenously. Berger and Schwartz[3] administered the drug orally and obtained a diminution of spasticity which was associated with a reduction or absence of abnormal muscular discharges on electromyograms. Their hemiplegic and spastic diplegic patients sustained an improvement of function in the paralyzed limbs without depression of voluntary power. However, Stephen

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† Supplied through the courtesy of E. R. Squibb and Sons under the name of "Tolserol."

and Chandy[18] administered the Tolserol intravenously and could not obtain relief of spasm in cases with spinal cord lesions.

Artane*, 3-(N-piperidyl)-1-phenyl-1-cyclo-hexyl-1-propanal hydrochloride, is one of the newer synthetic antispasmodic compounds[5]. Its pharmacological activity closely resembles atropine, but its parasympatholytic activity is less than that of atropine. In low doses it produces a mild depression of the central nervous system and in larger doses it causes an excitation which is common to the synthetic as well as the naturally occurring antispasmodic preparations.

The clinical effectiveness of Artane in reducing or abolishing the tremor and rigidity of Parkinson's disease had been observed by one of us[8]. However, Tolserol was relatively ineffective in this same group of Parkinson patients. In view of these data, the present study was undertaken to evaluate and compare the clinical effectiveness of both drugs in a variety of spastic neurological disorders. We here report on the therapeutic effect of Artane and Tolserol in 47 patients, all of whom had spasticity of one or more extremities.

Clinical Material and Method. There were 14 patients with hemiplegia or hemiparesis due to cerebral damage, 25 patients with paraplegia, paraparesis or tetraparesis due to spinal cord disease, and 8 patients with cerebral palsy. All but 6 cases were observed on the Neurological or Rehabilitation wards at Bellevue Hospital. These 6 cases were carefully followed at weekly intervals in the out-patient department (see Table 1).

Prior to the administration of drugs, each patient was given a medical examination, including careful neurological study and an evaluation of his ability to perform the functions inherent in daily living. These functions consisted of those activities considered necessary and most commonly performed during a 24-hour period. Each patient had a sufficient degree of spasticity and disability so that if the drug were therapeutically effective it could be noted subjectively and objectively. In no instance was a patient either improving or deteriorating rapidly enough to interfere with the clinical observations.

The therapeutic effectiveness of each drug was determined by the spontaneous subjective response of the patient as well as by objective criteria. When the patient reported subjective improvement, this result was checked by placebo medication. The objective criteria were determined by the change in resistance to passive stretch on moving the affected joint, or joints, through a full range of motion and the ability to perform, or to perform more easily, those activities previously tested. The results were confirmed by the independent observations of both authors.

Each drug was administered for a minimum period of 1 month. With Artane the initial daily dose was 2 mg., and this was progressively increased to a maximum of 20 mg. a day in 4 divided doses by the end of the 3rd week. The patient was then maintained on this maximum dose. Tolserol was administered orally as an elixir in every case; in addition, tablets or capsules were given either alone or to supplement the elixir. The initial dose was 1.5 gm. a day in 3 divided doses, and this was progressively increased to a maximum of 5 gm. a day in 5 divided doses. In a few cases as much as 1.5 gm. was administered every 3 hours (day and night) for 1 week. Eleven cases received Tolserol intravenously.

Results. The clinical results were classified into 4 groups (see Tables 2 and 3) as follows: Group A, no subjective or objective improvement; Group B, subjective improvement not maintained with placebo medication, or no subjective but slight objective improvement; Group C, definite subjective and slight objective improvement; and Group D, marked subjective and objective improvement.

HEMIPARESIS. A total of 14 patients with spastic hemiparesis due to cerebral disease were treated with Artane or Tolserol. Eleven of these patients received Artane, and 10 received Tolserol. Eight of these were given each of the compounds. With Artane, 6 patients had no subjective or objec-

* Supplied through the courtesy of Lederle Laboratories Division, American Cyanamid Co.

TABLE 1.—CLASSIFICATION OF 47 SPASTIC PATIENTS TREATED WITH ARTANE AND/OR TOLSEROL

Hemiparesis (14)	
Cerebro-vascular accident	8
Cranio-cerebral trauma	2
Intracranial neoplasm	1
Chronic arachnoiditis	1
Brain abscess (post-operative)	1
Chronic basal meningo-encephalitis	1
	14
Paraplegia, Paraparesis or Tetraparesis (25)	
Traumatic spinal cord injury	4
Erb's spastic paraplegia	3
Spinal cord neoplasm & vascular abnormalities	5
Multiple sclerosis	6
Chronic arachnoiditis	3
Undiagnosed spinal cord disease	4
	25
Cerebral Palsy (8)	
Tension athetoid	5
Spastic	3
	8
TOTAL	47

TABLE 2.—DEGREE OF IMPROVEMENT IN 42 SPASTIC PATIENTS TREATED WITH ARTANE

Type of case	*Number of cases*	*Group A**	*Group B**	*Group C**	*Group D**
Hemiparesis	11	6	4	1	0
Paraplegia, Paraparesis or Tetraparesis	23	16	2	5	0
Cerebral Palsy	8	5	2	1	0
TOTAL	42	27	8	7	0

* Group A: No subjective or objective improvement.
* Group B: Subjective improvement not maintained with placebo medication, or no subjective but slight objective improvement.
* Group C: Definite subjective and slight objective improvement.
* Group D: Marked subjective and objective improvement.

TABLE 3.—DEGREE OF IMPROVEMENT IN 41 SPASTIC PATIENTS TREATED WITH TOLSEROL

Type of case	*Number of cases*	*Group A**	*Group B**	*Group C**	*Group D**
Hemiparesis	10	4	4	2	0
Paraplegia, paraparesis or Tetraparesis	23	12	5	6	0
Cerebral Palsy	8	5	1	2	0
TOTAL	41	21	10	10	0

* See footnotes of Table 2.

tive improvement; 4 cases showed minimal improvement, which was subjective in 1 and objective in 3. One patient reported subjective improvement which was confirmed by a diminution of spasticity in the affected extremities but did not provide an increase in functional activities. With Tolserol, 4 patients had no subjective or objective improvements, 4 had only minimal objective improvement, and 2 showed slight improvement both subjectively and objectively. One of these patients with a severely painful frozen shoulder had definite relief of pain and increased passive range of motion at the shoulder joint.

Paraplegia, Paraparesis or Tetraparesis. Twenty-five patients with spasticity due to spinal cord disease were evaluated. Only the lower extremities were affected in 16 of these patients, and 9 had spasticity of the 4 extremities. Each compound was administered to 23 patients of this group, and 21 of them received both Artane and Tolserol at different times. Artane had no therapeutic effect in 16 patients. Two patients reported slight subjective improvement. Five cases had both subjective and objective improvement manifested by a reduction of spasticity. In 2 of the latter cases the improvement was translated into increased functional ability, so that the patients no longer dragged their feet heavily along the floor while walking. Tolserol had no therapeutic effect in 12 patients. Slight subjective as well as objective improvement in terms of decreased spasticity was recorded in 6 cases. In only 1 of these cases was the patient able to show any increase of functional ability, and that was only slight. In 2 of the 6 cases there was, in addition, a reduction of involuntary painful flexor spasms of the lower extremities.

Cerebral Palsy. Artane and Tolserol were administered at separate times to 8 cerebral palsy patients. Artane provided no beneficial response for 5 patients. Two patients reported subjective improvement, and 1 showed subjective as well as objective improvement. Again, the objective improvement was merely a diminution of resistance to passive stretch. With Tolserol, 5 patients had no therapeutic response, 1 reported subjective improvement, and 2 patients showed both subjective and objective improvement. One of the latter had difficulty in walking because of a marked scissors gait. With the Tolserol there was a mild diminution of spasticity and less crossing of the legs.

Five hemiparetics, 3 spinal cord cases and 3 cerebral palsy cases received Tolserol intravenously, 4000 to 6000 mg. of a 2% solution, at approximately 60 drops per minute. All patients became drowsy and most of them complained of feeling "drunk". Two patients to whom the infusion was given more rapidly became pale, nauseated and vomited several times. Of the hemiparetics, there was no clinical improvement in 1 patient, there was slight subjective improvement in 2, and the remaining 2 patients showed slight subjective and objective improvement not translatable into functional gains. Of the 3 spinal cord cases, 1 had no therapeutic improvement, a 2d had slight objective improvement as manifested by decreased spasticity, and a 3d showed both subjective and objective improvement as indicated by a similar diminution in spasticity plus the ability to walk without dragging his foot along the floor. Of the 3 cerebral palsy cases, 2 were tension athetoids in whom there was no therapeutic response, and 1 was a spastic who showed decreased spasticity but no functional improvement. All effects were transitory, and rapidly subsided soon after the infusion was discontinued.

Toxic Effects. *Artane.* Eleven (26.2%) of the 42 patients to whom Artane was administered complained of side effects. Eight of these patients had a feeling of lassitude. In only 3 patients, however, were the side effects sufficiently severe to require discontinuance of the medication: 1 had a marked anorexia. Another patient developed a papular rash, most marked over the chest, which disappeared when the drug was withdrawn and reappeared when the drug was given a 2d time but not a 3d time. A 40-year old man, who had been receiving 10 mg. of Artane a day in 3 divided doses, became confused and disoriented 3 days after the dose had been raised to 5 mg. t.i.d. He cleared mentally on the day after the medication was discontinued. Dryness of the mouth was an occasional complaint, but this action of Artane was an advantage in 2 of the cerebral palsy cases where sialorrhea was a complicating feature of the disease.

Tolserol. Nine (21.9%) of the 41 patients to whom Tolserol was administered complained of side effects, but these did not necessitate the discontinuance of the drug except for 1 case; in this patient, diarrhea recurred each of the 3 times the drug was administered. Seven patients complained of a slight feeling of dizziness beginning 15 minutes after the administration of the drug and lasting 30 to 60 minutes even with an individual dose as small as 0.5 gm.

Discussion. A review of the results of therapy with Artane and Tolserol demonstrates that both compounds are relatively ineffective in the treatment of spastic disorders. The positive responses obtained were consistently of a minimal degree and could be seen only by careful clinical observation. In no case was there an important improvement in function. In the entire group of 47 patients, it would be of slight advantage to the patient to continue medication in only 8 cases. One was the patient with cerebral palsy who obtained a diminution of adductor spasm as previously described. Two spinal cord patients had a reduction in painful involuntary flexor spasms. Two spinal cord patients and 1 hemiparetic had slight improvement in gait. One hemiparetic had decreased pain in a frozen shoulder, as already mentioned. In the case of chronic post-basal meningo-encephalitis, there was a reduction in the extreme restlessness and neck retraction. Tolserol was responsible for this minimal improvement in 7 of these cases.

Of the 36 patients who received each of the drugs, the results were equally ineffective in 30. In the remaining 6 cases, Tolserol provided a better response than Artane, but it is to be emphasized that this response was minimal.

The response to therapy could not be correlated with the etiology of the lesion, its level in the central nervous system or the degree of spasticity.

It is of interest that Tolserol was no more effective in alleviating the rigidity of Parkinson's disease than the types of spasticity described above. On the other hand, artane was therapeutically effective in approximately 70% of cases of Parkinson's disease[4,7,8], although of no therapeutic value in the spastic disorders.

Summary and Conclusions. 1. The effects of Artane and Tolserol were studied in 47 patients with spasticity due to disease of the central nervous system.

2. Both compounds were relatively ineffective in the treatment of spastic disorders.

3. There was no correlation between the response to therapy, the etiology of the lesion, its level in the central nervous system or the degree of spasticity.

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RECENT ADVANCES IN THE DRUG THERAPY OF PEPTIC ULCER*

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THE search for a drug capable of curing peptic ulcer continues to engage the interest of experimenters and clinicians alike. The literature persistently contains descriptions of new drugs and reports dealing with the effects of earlier introduced preparations. It is the purpose of this review to summarize current knowledge regarding some of the newer preparations and recently reported data pertaining to the action of some relatively older drugs which continue to attract clinical attention.

The bibliography at the end of this review has been arranged so that appropriate references appear separately for each of the drugs considered. No attempt has been made to present in its entirety the voluminous literature dealing with these drugs. Rather, certain references have been selected because they are considered representative of more recent reports, or because they are in themselves comprehensive surveys.

Banthine. Banthine (beta-diethylaminoethyl xanthene-9-carboxylate methobromide) is a quarternary ammonium salt with an anticholinergic action[7]. In the parasympathetic nervous system it not only blocks the transmission of impulses at the ganglionic synapse, but also exerts an atropine-like action at the post-ganglionic nerve endings. In the sympathetic nervous system its blocking action is only on the ganglionic synapse and larger amounts of the drug are required to produce this effect.

Experimental observations in animals and in man have demonstrated effective inhibition of gastrointestinal motility and reduction in gastric secretion fol-

* Drs. Herbert Hyman, S. Philip Bralow and Seymour Shore assisted in compiling the reports which serve as the basis for this review.

lowing oral or parenteral administration of the drug[4,7-9,10]. In general, the motor inhibitory action of banthine is more constant and predictable than its effects on gastric secretion[7,8]. Banthine markedly reduces fasting gastric secretion in dogs with vagally intact pouches[10], pyloric-ligated rats[9], normal human subjects[2,7,8], and duodenal ulcer patients[2,7,8,10,11]. It significantly inhibits the 24-hour gastric secretion in dogs with vagally intact whole stomach pouches while on a standard diet[10]. Histamine-stimulated gastric secretion may also be partially inhibited as shown in pouch dogs[2,10], normal human subjects[2], and duodenal ulcer patients[11]. The drug appears to have little or no inhibitory effect, however, on gastric secretion provoked by insulin hypoglycemia[8,10,11].

In comparison with atropine, the gastric motor inhibition produced by banthine in man appears to be more pronounced and longer lasting, particularly after oral doses of each drug[8]. The relative action of atropine and banthine in reducing volume and acidity of gastric secretion is more difficult to compare. Whatever advantage there may be, would seem to lie with banthine. Thus, Lyons and Grimson[8] found that in human subjects, ordinary clinical doses of banthine, parenterally or by mouth, reduced the volume and acidity of gastric secretion more consistently, to a greater degree, and for a longer time than equivalent doses of atropine. Benjamin, Rosiere, and Grossman[2] established a potency ratio of atropine to banthine for equivalent degrees of inhibition of histamine-stimulated gastric secretion of 1 to 20 in dogs with vagotomized pouches of the entire stomach, and of 1 to 8 in human subjects. In the latter, 1.2 mg. of atropine sulfate produced about the same inhibitory effect as 10 mg. of banthine, when both drugs were given subcutaneously. It should be noted that this is as large a dose of atropine as can ordinarily be tolerated by patients, whereas larger doses than 10 mg. of banthine may be given parenterally without producing intolerable toxic reactions. Shay, Gruenstein, and Jamison[9] found the inhibitory effects of atropine and banthine to be essentially equal in pyloric-ligated rats when both drugs were given subcutaneously in a dose of 0.3 mg. per 100 gm. of body weight. Doses of this magnitude given to an average man (210 mg. for a 70-kg. man) would be prohibitively toxic, although far less so for banthine than for atropine.

The gastric inhibitory action of banthine in man may be observed within 1 minute following intravenous injection, and within 20 to 30 minutes after oral ingestion. The degree and duration of inhibition vary with the dose and method of administration; inhibitory effects may persist as long as 6 to 8 hours following an oral dose of 100 mg., or 2.0 mg. per kg. of body weight[7].

Dryness of the mouth and blurring of vision are common side effects, especially with larger doses. These reactions tend to disappear or diminish as the drug is continued but at times are severe enough or troublesome enough to require reduction in dosage or even cessation of administration. Difficulty in bladder emptying is another fairly common side effect which may prove especially troublesome in patients with prostatic obstruction. There appears to be a wide range of safety between therapeutic and toxic doses. Save for behavior manifestations suggesting central nervous system stimulation in 6 patients with emotional instability[1], no evidence of chronic toxicity has yet been reported in patients receiving therapeutic doses of the drug. The tablets themselves are extremely bitter and the patient should be cautioned not to chew them.

In the treatment of ulcer disease, the

originally recommended dose was 100 mg. every 6 hours day and night. Growing clinical experience has made it clear, however, that smaller doses may be employed with equally effective subjective response in many patients. It has been recommended that as a prophylactic measure, half of the full therapeutic dose should be taken as maintenance therapy after apparent healing of the ulcer, with the patient instructed to revert to the full dose in the presence of unusual situational stress or in the event symptoms recur.

Clinical results obtained to date are highly encouraging[3,5,6,11]. However, evaluation should be reserved pending further trial and longer observation. It is already clear, and perhaps worthy of emphasis in view of the enthusiasm with which the drug has been clinically applied, that banthine, while useful and unquestionably valuable, is still not invariably effective and is attended by side reactions which make it intolerable to many patients.

Hexamethonium. Hexamethonium iodide (C6) is a member of a homologous series of polymethylene-bistrimethyl-ammonium compounds. The 3 members of this group which have been studied act alike in blocking the transmission of nerve impulses but appear to differ in their points of action. Compound C10 affects the neuromuscular junction of smooth muscle, thereby exerting a curare-like action. Compound C5 acts mainly at the preganglionic sympathetic synapses and is a vasodilator. Compound C6 does not exhibit a curare-like action and has no marked effect on blood pressure but appears to have a profound effect on gastric secretion and motility.

Very few observations have been made to date on this interesting blocking agent. Following intramuscular injection of 100 mg. of C6, fasting gastric secretion fell immediately in each of 10 patients with duodenal ulcer and was followed by a period of complete achlorhydria[13]. In most cases the fall in gastric acidity persisted for about 4 hours. In these same ulcer patients C6 prevented to some extent the expected secretory response to insulin but did not alter the response to histamine. When the compound was given in a dose of 100 mg. intramuscularly every 4 hours, the volume of night secretion was reduced by more than half and acidity was markedly lowered.

These same observers also reported[14] that intragastric instillation of 500 mg. of C6 in 10 fasting duodenal ulcer patients resulted in achlorhydria in 5 and a substantial fall in acidity in 3. They found that all hexamethonium halides successfully reduced gastric secretion, with the iodide and bromide exceeding the chloride in degree of effectiveness.

In contrast to these observations, Douthwaite and Thorne[12] found that 100 mg. of C6 given intramuscularly to 7 duodenal ulcer patients lowered only slightly the acid curves in 6 of the 7 after a gruel test meal. Only one of the 7 displayed achlorhydria and in this case the control acid curve was low. Similarly, Scott and his associates[15] found that the acid level in 6 of 10 duodenal ulcer patients was unaffected by a test dose of C6 and that in these same 10 patients interval gastric analyses during continuous treatment with C6 showed no evidence of progressive diminution. Shay, Gruenstein, and Jamison[16] found that aside from a decrease in output of total hydrochloric acid, C6 had no significant effect on fasting gastric secretion in pyloric-ligated rats.

The effect of C6 on motor activity of the stomach appears to be significant. Complete inhibition of gastric motility for from 3½ to 4½ hours was noted in records obtained in 10 active duodenal ulcer patients[13]. Another group of 7 patients with duodenal ulcer showed notable delay in gastric empty-

ing of a barium meal when 100 mg. of C6 was given intramuscularly ½ hour before the meal[12].

Side effects are fairly common and may be distressing. Suffusion of the conjunctiva is almost constant and may appear within a few minutes. Syncope and faintness accompanied by a fall in blood pressure and an elevation in pulse rate on standing appear to be common[12,13,15]. Blurring of vision and dryness of the mouth are other reactions described by some patients. In general, these side effects tend to become less pronounced as administration of the drug is continued.

Clinical observations of the therapeutic effect of C6 in duodenal ulcer is limited at this time to 1 group of 10 patients[15]. All were given an ordinary diet, with alkali as needed for severe pain, and 500 mg. of hexamethonium bromide by mouth at 8 a. m., 2 p. m. and 8 p. m. Of the 10, 6 completed a 24-week course of treatment. Four were greatly improved, 2 continued to have mild symptoms, 1 defaulted after 8 weeks, 1 developed pyloric stenosis after 7 weeks, and 2 suffered severe relapses after initial improvement. Clinical improvement was not always accompanied by demonstrable reduction in gastric acidity.

Though these results were much better than those obtained in a control group of 10 patients given a placebo, they are not impressive. A great many more patients must be observed and further studies carried out before this drug can be evaluated.

Tetraethylammonium. Tetraethylammonium (chloride or bromide) is still another blocking agent which has been applied in peptic ulcer therapy. It prevents transmission of impulses from the preganglionic fibers to the ganglion cells in both the sympathetic and parasympathetic nervous systems. Gastric secretion and gastrointestinal motility have been shown to be reduced effectively following intravenous or intramuscular administration of the drug[18,20,22,25]. The duration of effect varies with the dose, but pre-existing secretory and motor status is ordinarily recovered within 3 hours.

More recently it has been shown that tetraethylammonium chloride, given intravenously to dogs in a dose of 10 mg. per kg. of body weight, 1) markedly decreases the gastric secretory response to sham feeding, 2) decreases gastric secretion induced by insulin hypoglycemia, 3) decreases the gastric secretory response to mechanical distention, 4) has no effect on histamine-induced gastric secretion, and 5) significantly inhibits gastric secretion provoked by 0.05 mg. of urecholine given parenterally every 10 minutes, but does not influence gastric secretion following doses of 0.1 mg. of urecholine every 10 minutes[23]. The fasting gastric secretion of pyloric-ligated rats, on the other hand, is apparently not affected by tetraethylammonium[24].

Gastroscopic observations in 10 patients given 200 mg. of tetraethylammonium chloride intravenously showed that within 30 to 90 seconds after injection of the drug the gastric mucosa became pale, and within 3 to 5 minutes became maximally blanched. Simultaneously, peristalic activity diminished and finally stopped, and the gastric rugae became flat[21].

Earlier reports of clinical effectiveness of tetraethylammonium in relieving pain in patients with peptic ulcer[19] have been confirmed[17]. It still seems that the greatest field of usefulness of this drug in ulcer therapy is in the management of the ulcer patient with night pain or of the patient with severe acute distress requiring immediate relief. Postural hypotension continues to be the principal problem with respect to side reactions.

Dibutoline. Dibutoline (dibutylurethane of dimethylethyl-beta-hydroxy-

ethyl ammonium sulfate), a choline derivative, exerts a depressant effect on the postganglionic receptor substance. In normal human subjects and patients with peptic ulcer, parenteral administration of the drug significantly reduces gastric motor[26,29] and secretory[28,29] activity. Fasting gastric secretion in pyloric-ligated rats is also significantly diminished after subcutaneous injection of dibutoline[30]. For effective results the dose in man should be of the magnitude of 30 mg. (20 to 40 mg.). The use of doses smaller than this may account for failure to obtain better gastric depressant action in some studies[27].

The drug has the advantage of acting within a few minutes after subcutaneous injection. It has the additional advantage over atropine of producing fewer and less marked side reactions. In degree of effectiveness it compares favorably with atropine and even with banthine in respect to reduction in gastric motor activity[29]. It appears to be somewhat less effective than atropine and definitely less effective than banthine in depressing gastric secretion[29,30].

The duration of action of dibutoline is not long. Ordinarily, depressant effects of the drug become dissipated within 2 to 3 hours after administration, so that repeated doses are required at 3-hour intervals. Moreover, the drug is ineffective when given by mouth[29]. These disadvantages militate against its widespread adoption as a therapeutic agent in ulcer management.

ACTH and Cortisone. The application of pituitary adrenocorticotropic hormone (ACTH) and cortisone to the treatment of chronic gastroduodenal ulcer stems in part from bits of evidence suggesting the possibility of a pituitary–gonadal mechanism in the pathogenesis of peptic ulcer[35,37], and in part from reasoning from association. Pregnancy, as a rule, has an ameliorating effect on the symptoms of peptic ulcer as well as on those of rheumatoid arthritis. Since cortisone and ACTH are apparently beneficial in the latter disease[34], it was reasoned that these materials might prove equally beneficial in ulcer disease[37].

Support for this hypothesis was afforded by observations indicating that patients with duodenal ulcer excrete significantly lower amounts of 11-oxycorticosteroids during periods of ulcer distress than do normal subjects or the same ulcer patients during symptom-free periods[37]. Initial observations in a series of Mann–Williamson dogs (dogs operated on in such a fashion that jejunal ulcer develops) appeared to lend further support to the hypothesis[37]. The average postoperative survival time of animals treated with cortisone was approximately 40% longer than that of animals treated with ACTH and twice that of the control animals. At the time of the report, only 1 of the 11 control dogs had survived for 6 months after operation, whereas 4 of the 6 cortisone-treated dogs and 2 of the 6 ACTH-treated dogs were still alive at the end of 6 months. However, histologic examination of the ulcers in the ACTH and cortisone-treated Mann–Williamson dogs failed to disclose evidences of healing or other changes significantly different from those in the untreated control animals[36].

Standing in contrast with these observations is a growing body of evidence indicating that ACTH and cortisone may not only be ineffectual but may actually be harmful in ulcer disease. Administration of 100 mg. of ACTH daily to normal subjects results in an immediate and marked increase in 24-hour excretion of uropepsin, an enzymatic substance present in urine and believed to originate from pepsinogen, the precursor of gastric pepsin[39]. ACTH given to patients with active peptic ulcer in doses of 40 mg. daily

also produced an impressive rise in uropepsin excretion, although the increase did not appear until about the seventh day of treatment. ACTH, given by Gray and his associates[32] to experimental subjects in doses of 80 to 120 mg. daily for from 10 to 21 days, produced an immediate and marked increase in 24-hour urinary excretion of uropepsin and a significant rise in gastric juice pepsin within 7 to 14 days. An identical rise in uropepsin excretion was also observed following the administration of cortisone orally or intramuscularly. Of interest is the observation by these investigators that elevated uropepsin excretion followed repeated injections of 0.6 mg. of epinephrine at 6-hour intervals for 4 days. This rise was associated with a significant fall in the level of circulating eosinophils.

Reports have appeared of lack of response of duodenal ulcer symptoms to cortisone[37] and of aggravation of symptoms, hemorrhage, and perforation following prolonged administration of ACTH[31,33,37,38]. A disconcerting feature in these patients is the obscuring effect of ACTH on the clinical signs of perforation. Temperature elevation is relatively low, leukocytosis is minimal, and abdominal rigidity may or may not be present despite the presence of diffuse peritonitis.

On the basis of the available evidence, therefore, it would appear that cortisone is not to be recommended for use in ulcer patients and ACTH is definitely contraindicated in this disease.

Enterogastrone (Enteroanthelone). Enterogastrone, a hormonal agent elaborated by the intestinal mucosa when in contact with fat or sugar, inhibits motor and secretory activity of the stomach. Potent extracts of hogs' intestine have been prepared which significantly depress gastric secretion in dogs when given intravenously, presumably because they contain enterogastrone. This property encouraged the trial of such concentrates in ulcer therapy.

Available enterogastrone concentrates cannot be administrated safely to man intravenously. When administered by other routes, past efforts to inhibit gastric secretion in man have failed to produce significant or even predictable results[48]. Recently reported efforts along this line have proved equally unsuccessful[41,46,49].

Administration of enterogastrone concentrates to Mann–Williamson dogs, subcutaneously and intramuscularly, appeared to have beneficial healing and immunizing effects on this type of experimental ulcer, *without* inhibiting acid secretion. This led to the concept that these concentrates contain an anti-ulcer component for which Sandweiss suggested the name "anthelone" (anti, against; helkos, ulcer).

The beneficial results obtained by Ivy and his associates with their specially prepared enterogastrone concentrate in Mann–Williamson dogs prompted Greengard and his co-workers to employ the material in ulcer patients. The immediate clinical results appeared to be encouraging. However, subsequent studies by others employing commercial preparations of enteroanthelone parenterally as well as by mouth resulted in little or no benefit, either in ulcer patients or in Mann–Williamson dogs[48]. Still more recent reports confirm the ineffectiveness of present commercial preparations of enteroanthelone, both in Mann–Williamson dogs[47] and in ulcer patients[40,42].

In addition to the enterogastrone concentrate specially prepared by Ivy and his associates in their laboratory, and the commercial preparations used by the other workers cited above, still other musosal and submucosal extracts of hogs' stomach and duodenum, desic-

cated and defatted raw whole mammalian duodenum ("Viodenum"), and unspecified protein-free preparations of stomach and small intestine ("Robuden")[44] have been prepared and employed in the treatment of ulcer. Recent studies indicate that these preparations likewise are without benefit in ulcer patients[45,50,51].

It is important to note that differences may exist in the various preparations of enterogastrone concentrates which may significantly affect or alter their action in man or other animals[43].

Urogastrone (Uroanthelone). Urogastrone is a hormone-like gastric secretory depressant present in urine. Its name is derived from its close resemblance in action to enterogastrone. Like enterogastrone, it has an inhibitory effect on gastric secretion when given intravenously to dogs, but does not significantly or consistently alter gastric secretion when given subcutaneously or intramuscularly to man[54]. As in the case of enterogastrone concentrates, it likewise has prophylactic and therapeutic effects on Mann–Williamson ulcers in dogs, *without* influencing gastric secretion[54]. The anti-ulcer factor responsible for these effects has been designated "uroanthelone" to distinguish it from the anthelone present in intestinal extracts.

Previous efforts at treating ulcer patients with uroanthelone prepared from human pregnancy and nonpregnancy urine yielded encouraging immediate clinical results, but the recurrence rate after therapy was stopped proved to be disappointingly high[54].

The most recent preparation to appear is "Kutrol", an extract prepared from freshly collected, mid-term pregnant mares' urine. The buff-colored amorphous powder present in each capsule contains 75 mg. of extract representing the material derived from 300 to 900 cc. of urine. The recommended dose in the treatment of ulcer disease is 2 capsules 4 times daily, ½ hour before meals and at bedtime.

Studies in ulcer patients indicate that the material does not alter gastric secretion when taken by mouth[52], although it is alleged to have an inhibitory effect on gastric secretion in the pyloric-ligated rat[53]. Oral administration of Kutrol to Mann–Williamson dogs by Sandweiss and his co-workers significantly prolonged survival time and reduced the incidence of ulcer formation[55]. Clinical results over a 20-month period in 26 specially selected duodenal ulcer patients have been reported by Page and Heffner[53]. Of 16 patients with duodenal ulcer resistant to conventional treatment, 15 responded favorably, becoming symptom free in an average of 4 to 6 weeks and showing disappearance of the ulcer crater on Roentgen-ray examination; all 7 patients with chronic jejunal ulcer responded favorably; only 1 of 3 patients with chronic perforating duodenal ulcer was improved. Berkovitz, and Sandweiss and his associates, have also treated patients with Kutrol. Their observations are still continuing and are as yet unreported. The immediate clinical results which they have obtained, however, appear to be encouraging[54].

Despite these promising experimental and clinical results, the ultimate evaluation of Kutrol requires further observation and additional studies.

Sodium Carboxymethylcellulose. Sodium carboxymethylcellulose is a salt of a weak organic acid (carboxymethylcellulose) and a strong base (sodium hydroxide). It was selected after a systematic investigation of various polycarboxylic acids as the one closest approaching the requirements for an ideal antacid[59]. One gram of the material is capable of combining with 40 cc. of 0.1-N hydrochloric acid. It goes into solution slowly by first passing through a gel stage and then forming a viscous

solution which adheres tenaciously to the mucosal surface. Gastric acidity may be buffered in 2 ways: 1) by exchange of sodium ions for hydrogen ions when the material is in the gel stage; 2) by true buffer action when the material goes into solution. Reduction in gastric acidity is moderate in degree so that alkalinization and acid rebound do not occur. No change is produced in acid–base balance, since the anion exchange which occurs in the stomach is reversed in the alkaline intestine. The tenacious adherence of the viscous solution affords not only local protective coating, but is thought to contribute to a diminution in volume of gastric secretion. Because of its nonabsorbability and affinity for water, the drug has the added advantage of acting as a hydrophylic bulk laxative.

Side effects are reputedly few. No signs of toxicity were observed in animals and humans who received the drug for long periods[59]. The local healing properties of the compound were demonstrated by its beneficial effects on skin wounds in guinea pigs. The incidence of histamine-induced ulcers was significantly reduced in dogs treated with sodium carboxymethylcellulose as compared with controls[59].

Initial clinical results in ulcer patients treated with sodium carboxymethylcellulose appear to be favorable but not particularly impressive[57, 58]. Of 105 ulcer patients observed over a period of 1 year after institution of treatment with tablets containing 450 mg. of sodium carboxymethycellulose and 150 mg. of magnesium oxide, Bralow and his co-workers found that 23% had to be readmitted to the hospital because of recurrent pain, hemorrhage, or perforation, while 61% had remained entirely asymptomatic[57]. These results were in contrast with those in a control group of 100 patients treated with aluminum hydroxide gel. In the latter group over the same period of time, 34% required readmission to the hospital and 40% remained asymptomatic.

The drug has been made commercially available as "Carmethose". It is prepared as a 5% aqueous solution, and as tablets, each tablet containing approximately 225 mg. of sodium carboxymethylcellulose and 75 mg. of magnesium oxide. The recommended dose is from 2 to 4 tablets 4 to 6 times daily, or, if necessary, every 2 hours. It should be pointed out that the content of the commercial tablets is only one-half that used by Bralow and his associates. It should also be noted that the product employed for investigative purposes by Bralow *et al.* was composed of the "gamma" form of carboxymethylcellulose, whereas Carmethose contains the "alpha" form[56]. The former is soluble in 0.1-N hydrochloric acid but the latter is not. Despite this, no notable differences in immediate clinical effects were noted in small groups of ulcer patients given both products or treated alternately with each form[56]. It has been hypothesized that the gamma preparation acts principally in the stomach and the alpha, in the duodenum.

Considerable further study is required before this drug can be evaluated.

Protein Hydrolysates. The emphasis placed a few years ago on hyperalimentation therapy of peptic ulcer using casein hydrolysate[60] has largely subsided. It is now generally agreed that protein requirements may adequately be met in most ulcer cases by supplying a minimum daily intake of 100 gm.[66].

From the standpoint of the ability to digest protein of the average patient with uncomplicated gastroduodenal ulcer, there would appear to be no need to supply other than whole or native protein. From the standpoint of antacid action and buffer capacity, however, recent studies[62,65] confirm the superiority of hydrolyzed protein over

milk[63] and indicate that a combination of protein hydrolysate and milk is even more effective than hydrolysate alone[62]. A partial explanation for some of the inconsistencies obtained by previous investigators, and one reason for the apparent imperfection of protein hydrolysate as a buffer and neutralizer of gastric and duodenal bulb acidity[63], may be variation in the rate of gastric emptying. Sun and Machella[67], employing hourly feedings of 30 gm. of a casein hydrolysate in 20 ulcer patients and 2 patients with chronic gastritis, succeeded in maintaining an absence of free acid in only one-half of the patients throughout the 14 hours the preparation was administered. In the 11 cases in which the hydrolysate mixture failed to neutralize free acid thoughout the observation period, the average rate of gastric emptying was more rapid than in those with maintained achlorhydria.

Recent studies of groups of ulcer patients treated with hydrolyzed protein have yielded opposite results with respect to symptomatic response. Morrison[64] fed a hydrolysate in milk or water every 1½ hours to 20 patients and found that all but 2 improved. Distress was relieved in approximately one-half the time required by a control group treated by conventional means. Kay, Jamieson, and Smith[61], on the other hand, gave an enzymic hydrolysate of milk to 2 groups of ulcer patients; 1 received a tablespoonful of the preparation 3 times daily while the other received hourly feedings of 4 tablespoonfuls in water for 1 week and then was fed the material only between meals. In the first group, comprising 16 patients, the results were very poor; in the second group, made up of 7 patients, only 1 improved and 1 was questionably improved. All patients in both groups, however, showed a gain in weight.

Anion Exchange Resins. Efforts are continuing to improve the quality and effectiveness of these insoluble plastic substances. Newer resins are being constantly sought and attempts are continually being made to reduce particle size and thereby improve the neutralizing capacity of these drugs.

Reports also continue to appear attesting to the clinical efficacy of the anion exchange resins[68,70-72,74]. Hall and Hornisher[68] compared the time required for duodenal ulcer craters to heal in 17 patients given aluminum hydroxide gel with that in 33 patients treated with an anion exchange resin ("Resinat"). The average healing time in the resin-treated cases was 19 days, while the average time in the aluminum hydroxide gel-treated group was 33.7 days. Wirts, Sullivan, and Hemmerly[74] found that on the basis of time required to relieve symptoms, incidence of unresponsiveness, and average healing time as shown by Roentgen-ray examination, in a group of 44 ambulatory out-patients with duodenal ulcer and 24 semiambulatory ward patients treated alternately with anion exchange resin or aluminum hydroxide gel, the clinical effectiveness of the resin was comparable to that of the gel but did not notably surpass it. Similarly, Segal *et al.*[71] secured a clinical remission in 65% of 26 patients with chronic recurrent duodenal ulcer treated with an anion exchange resin, but failed to obtain clinical remissions in 6 patients with intractable lesions, 5 with penetrating ulcers, and 4 with partial obstruction.

Further studies have been made of the *in vivo* neutralizing effect of anion exchange resins[69,71,73]. Resinat in amounts of 1.0 gm. orally significantly reduced histamine-stimulated gastric free acid for 1 hour after its administration to a mixed group of ulcer and nonulcer patients[69]. When compared with the effects of other drugs studied in the same

manner, notably aluminum hydroxide gel ("Amphojel") and a combination of aluminum hydroxide, magnesium trisilicate, and mucin ("Mucotin"), no consistent difference in effectiveness was found. Amberlite IR-4 was shown by Wirts and Rehfuss[73] effectively to neutralize gastric free acid and inactivate pepsin in both ulcer and nonulcer subjects following insulin and repeated histamine stimulation. The resin also caused a substantial reduction in free acid and pepsin and a rise in pH in the duodenal bulb in both ulcer and nonulcer patients after repeated histamine stimulation. There appeared to be no rebound rise in gastric acidity. The antacid effects of the resin in these experiments were comparable to those produced by aluminum hydroxide and a modified Sippy powder. However, the dose of resin employed was 3.2 gm., a considerably larger single dose than that ordinarily employed in ulcer therapy.

With respect to dosage, Segal and his associates[71] have presented data to indicate that at least 2.0 gm. of powdered resin are necessary to elevate gastric pH consistently. They point out, in view of this, that the amounts of resin employed by those who have previously reported on the clinical effectiveness of these substances (0.25 to 0.5 gm. hourly or 0.5 to 1.0 gm. every 2 hours) are too small to have produced an adequate decrease in gastric acidity.

From the theoretical standpoint, anion exchange resins would appear to have much merit. Yet, clinical experience with these preparations in the management of ulcer disease has not been overly impressive. Continued improvement in the product may eventually succeed in raising the clinical efficiency of these promising materials.

Drug Combinations. Numerous combinations of drugs have been devised and employed in ulcer management in the hope of enhancing pharmacological effects or perhaps offsetting an undesirable action of one compound by the opposing action of another. "Carmethose", one of newly introduced drugs discussed earlier, represents a combination of sodium carboxymethylcellulose and magnesium oxide. The latter is believed to have a potentiating effect on the former, so that the combination is more efficacious than the sodium carboxymethylcellulose alone.

Recent years have witnessed a revival of interest in gastric mucin with a growing trend to combine this substance with antacids or other drugs. One such preparation, introduced several years ago but still the subject of study and report, is a combination of aluminum hydroxide, magnesium trisilicate, and gastric mucin ("Mucotin"). Hardt and Steigmann[75] report their observations in a group of 125 ulcer patients followed from 6 months to 2 years. Mucotin was given 1 hour before meals, 1 hour after meals, and at bedtime, but some patients with severe symptoms were given hourly doses. Of 85 patients treated for longer than 1 year, 53 (62%) were completely relieved and had no recurrence.

Another mucin-containing preparation on which observations have recently been reported is a combination of gastric mucin and a polyamine anion exchange resin ("Resmicon"). Steigmann and Schlesinger[78] describe studies made by them in 30 patients with duodenal, gastric, or marginal ulcers. Administration of 2 or 4 Resmicon tablets simultaneously with injection of histamine to previously intubated fasting patients resulted in a lowering of the acid level below that obtained in control observations using histamine alone. The results were interpreted to indicate that the addition of mucin enhances the antacid effects of the resin. However, in an earlier report shared by one of the present investigators[76], the antacid action of a

mucin–resin combination was found to be no more effective under the same experimental circumstances than resin alone (Resinat), aluminum hydroxide gel (Amphojel), or a combination of aluminum hydroxide, magnesium trisilicate, and mucin (Mucotin).

Clinical observations in the same group of patients during, and for varying periods after, treatment with Resmicon showed that "most" patients had good symptomatic relief within 2 to 7 days after the start of therapy. Most of the patients apparently took the tablets well, although 2 objected to their taste. Twenty of the 30 patients remained free of distress during observation periods which ranged from 6 to 15 months. Objective evidence of ulcer healing by Roentgen-ray examination and gastroscopy was obtained within 2 to 4 weeks in most cases.

The most recent combination introduced into clinical practice is "Chloresium Powder". This is a combination of water-soluble derivatives of chlorophyll, aluminum hydroxide, and magnesium trisilicate in a powdered okra base. The chlorophyll was purposely included for its tissue-repairing properties while the okra was incorporated to supply a mucilaginous character to the mixture.

Offenkrantz[77] treated 79 ulcer patients with this preparation. One powder (containing 1.8 gm.) was given 5 times daily, on arising, 1½ hours after meals, and on retiring. Fluids or solids were avoided for a period of 1½ hours after the powder was taken. The length of treatment extended from 2 to 8 weeks with the majority receiving treatment for 3 to 4 weeks.

Five of the 79 cases had pyloric obstruction which failed to improve and were operated upon. Of the remaining 74 cases, 60 (81%) experienced complete symptomatic relief within 1 to 3 days after treatment was begun. Complete healing, as shown by Roentgen-ray examination, occurred in 58 of the 74 after 2 to 7 weeks of treatment. No recurrences took place over follow-up periods ranging from 4 to 11 months in the 20 patients who showed complete healing of their ulcers by Roentgen-ray examination. In no case was there obvious evidence of toxicity nor was there a tendency toward constipation or diarrhea.

Discussion. It is apparent from the foregoing data that a specific cure for peptic ulcer is still not at hand. The search in recent years appears to have turned from antacids to compounds which are antisecretory, or which may, through devious and poorly understood mechanisms, enhance the natural resistance of the gastroduodenal mucosa. These avenues of approach appear to have resulted in definite gains, and prosecution of further studies along these lines is definitely warranted.

Surprisingly little attention has been given to the action of drugs on the contents of the duodenal bulb where most clinical ulcers occur. Available evidence indicates that in the presence of active duodenal ulcer there is a definite derangement of certain duodenal mechanisms[79,82,83]. The possible correction of these by drugs presents still another avenue of approach worthy of investigation.

The data appearing in recent years are generally of a superior character. There is evident in the formulation and prosecution of these studies an awareness of the pitfalls which attend the evaluation of any drug used in the treatment of a disease as perplexing as peptic ulcer. Even so, justifiable criticism may be leveled at many of the reports which have appeared.

It is still inadequately realized that the measure of effectiveness of a drug, or any other therapeutic measure employed in ulcer disease, is not alone the relief of symptoms. An appreciable percentage of patients with uncomplicated

gastroduodenal ulcer respond with subjective improvement to a variety of placebos[80,81,84]. Indeed, such placebos may actually be accompanied by objective alterations in the motor and secretory activity of the stomach and duodenum[84]. Many of the drugs recently applied to the treatment of peptic ulcer bring about subjective improvement which, in terms of percentages, is no greater than, and is often less than, that obtained with conventional measures of ulcer management. Yet, control groups treated with placebos and with a more orthodox regimen are all too frequently omitted in studies designed to evaluate the therapeutic effectiveness of a new medicinal agent.

Careful appraisal of the gastroscopic and roentgenologic appearance of the ulcer defect during treatment is too often neglected. This is particularly regrettable, since these represent the principal measures of the healing rate and the effects of a given drug on this rate.

Follow-up observations are in many instances a matter of only a few weeks and only rarely are they pursued longer than a few months. Under these circumstances, the ability of a given drug to diminish recurrence rate cannot be properly evaluated.

The change in the type of drugs being studied has fortunately been associated with wider use of *in vivo* rather than *in vitro* studies. While these of necessity have been conducted in experimental animals, it is important to note that the animals employed are not naturally prone to develop gastroduodenal ulcer or that they have been equipped with an artificially induced ulcer not entirely akin to that seen in man. Consequently, the results obtained in these animals may not be unqualifiedly transferred to man. Even when human subjects are used as the source of reference for the action of a medicinal agent, the results may not be applied without qualification if the subjects are free of ulcer disease and if they do not have the secretory and motor changes characteristic of the patient with an active gastroduodenal ulcer.

These and other intangibles having to do with the influence of suggestion and enthusiasm on the part of both patient and physician make evaluation of drugs particularly difficult in peptic ulcer. Awareness of these limitations and adoption of an attitude of vigilant and critical skepticism should do much to clarify the role of drugs in this disease.

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RADIOLOGY

UNDER THE CHARGE OF
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ROENTGENOLOGIC DIAGNOSIS OF CONGENITAL CARDIOVASCULAR MALFORMATIONS

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IN the past two decades there has been a remarkable upsurge in the interest in congenital malformations of the heart and great vessels.

Surgical corrective measures developed by Blalock[4], Taussig[4], Brock[6], Potts[40], Gross[25], Crafoord[12], and others have completely changed the outlook on this group of diseases. Prior to this time the medical profession in general regarded the study of congenital heart disease as rather academic. The patient was characterized as having a relatively rare and obscure condition whose treatment was symptomatic and prognosis generally unfavorable. Too often the postmortem examination was the only reliable diagnostic method.

Now a premium is placed on accurate, detailed diagnosis as early as possible in the patient's life. To cope with the numerous perplexing problems many large medical centers have fostered the co-operative activity of outstanding cardiologists, radiologists, and surgeons. Indeed, in a few places there are highly specialized teams concerned solely with cardiac catheterization and angiocardiography.

General Incidence. The opinion has been expressed that after the first flurry of surgical correction of congenital heart disease the supply would rapidly decline to an irreducible minimum which would then constitute a stable but relatively unimportant group of patients. At least 2 factors are at work to controvert this opinion. The first factor is the increased knowledge and interest on the part of the medical profession. Many cases previously unrecognized are now brought to light. The second factor is the perfection of newer surgical techniques to expand the categories of remediable cases.

Congenital heart disease deaths[24] occur mainly in persons under 5 years of age. In that age group it accounts for 91% of the mortality from all forms of heart and closely related diseases. The death rate in this country is 5.8 per 100,000 males and 4.5 per 100,000 for females. There are differences between the urban and rural rates and also differences between the rates in the Northern states and in the Southern states. These small differences, however, are not believed to be signifi-

cant and may well be related to the availability of medical personnel and facilities. The mortality curve for congenital heart disease shows a rapid decline after its peak in the youngest age group. Despite this fact, congenital heart disease mortality is of greater magnitude than deaths from syphilitic heart disease, acute endocarditis, and acute rheumatic fever. Almost 8,000 deaths per year can be attributed to congenital heart disease.

Classification. Various schemes of classifying congenital malformations of the heart have not yielded one that is universally satisfactory[20,44]. The basis for most classifications is the presence or absence of cyanosis. Several schemes are presented, each of which has its particular virtues. Abbott's[1] classification is as follows.

Group 1. Acyanotic. No Abnormal Communications. This group comprises those without abnormal communications between the right and left side of the heart; thus, cyanosis is not part of the picture. Examples are as follows: 1) anomalies of the aortic arch and its branches; 2) coarctation of the aorta; 3) anomalies of the aortic valves; 4) endocardial anomalies: a) subaortic stenosis; b) aberrant chordae; 5) hypertrophy of the heart in infants; 6) anomalies of the coronary arteries; 7) simple dextrocardia; and 8) pericardial anomalies.

Group 2. The Arteriovenous Shunt with Terminal Reversal of Flow. This group embraces patients with arteriovenous shunts, in whom arterial blood enters the pulmonary circulation. Cyanosis is usually not observed. There is, however, a possibility of reversal of flow with the appearance of cyanosis, especially in patients who develop pulmonary hypertension or cardiac decompensation. Examples are: 1) patent ductus arteriosus; 2) atrial septal defects and patent foramen ovale; 3) ventricular septal defects; and 4) aortic septal defects.

Group 3. Congenital Cyanosis with Permanent Venous-Arterial Shunt. This group includes patients in whom cyanosis is a prominent feature. Among the many entities are the following: 1) tetralogy of Fallot; 2) tricuspid stenosis; 3) Eisenmenger's complex; 4) isolated pulmonary stenosis; 5) cor biloculare and triloculare; 6) truncus arteriosus; and 7) transposition of the great vessels.

A useful radiologic classification may be made on a basis of cyanosis, the size of the pulmonary conus, and the size of the pulmonary arterial segment. This system has been suggested by Peck and Wilson[39]. The following classification embodies the 3 factors: cyanosis, size of pulmonary conus and pulmonary arterial segment, and the status of the parenchymal pulmonary vascularity.

For the sake of convenience a partial alphabetical listing of the major congenital malformations of the heart and great vessels may be useful. It is also thought useful to append a rough approximation of the relative frequency of the various anomalies. The frequency is given in per cent and is divided into those in which the entity is the primary lesion and those in which the entity is an associated anomaly. Maude Abbott's[1] "One Thousand Proven Cases" forms a basis for this approximation.

General Considerations. Throughout this review the words atrium and auricle will be used interchangeably. In describing septal defects it is believed to be redundant to use the prefix "inter" with atrial and ventricular septal defects.

There has also been considerable difficulty in describing the main pulmonary arterial trunk just before it divides into the right and left pulmonary arteries. It has been variously called

TABLE 1.—CLASSIFICATION OF CARDIAC ANOMALIES AS TO CYANOSIS, SIZE OF PULMONARY CONUS AND ARCH, AND PROMINENCE OF LUNG VESSELS.

Anomaly	*Size of Pulmonary Conus and Pulmonary Arch*	*Prominence of Pulmonary Vascularity*
CYANOTIC		
1) Tetralogy of Fallot	Diminished	Diminished
2) Tricuspid atresia	Diminished	Diminished
3) Truncus arteriosus (pseudo)	Diminished	Diminished
Truncus arteriosus (true)	Diminished	Normal
4) Transposition of the great vessels	Diminished	Increased
Transposition (Taussig-Bing type)	Increased	Increased
5) Isolated pulmonary stenosis	Increased	Diminished
6) Eisenmenger's complex	Increased	Increased
ACYANOTIC		
1) Atrial septal defect	Increased	Increased
2) Ventricular septal defect (large)	Increased	Increased
3) Patent ductus arteriosus	Increased	Increased
4) Lutembacher's complex	Increased	Increased
5) Eisenmenger's complex	Increased	Increased
6) Coarctation of the aorta	Normal	Normal
7) Ventricular septal defect	Normal	Normal
8) Aortic and subaortic stenosis	Normal	Normal

TABLE 2.—ALPHABETICAL LIST OF MAJOR CONGENITAL MALFORMATIONS OF THE HEART AND GREAT VESSELS.

Malformation	*Relative Frequency % Classified as Primary Lesions*	*Relative Frequency % Associated With Other Anomalies*	*Total %*
Aortic arch anomalies including aberrant subclavian vessels	3.0	4.9	7.9
Atrial septal defects	7.3	30.0	37.3
Biloculate heart	0.9	0.5	1.4
Triloculate heart biatrium	1.3	1.4	2.7
Triloculate heart biventriculare	0.5	1.0	1.5
Coarctation of the aorta	7.0	3.5	10.5
Infantile type	0.9	2.8	3.7
Coronary, aberrant	0.8	0.2	1.0
Dextrocardia	2.9	1.0	3.9
Lutembacher's complex	0.6	1.7	2.3
Patent ductus arteriosus	9.2	15.0	24.2
Aneurysm	1.3	0.7	2.0
Pulmonary arteriovenous fistula	0.6	0.2	0.8
Pulmonary stenosis, isolated	2.5	0.6	3.1
Tetralogy of Fallot	11.5	5.4	16.9
Transposition of the great vessels	6.5	4.0	10.5
Tricuspid atresia	1.9	1.9	3.8
Truncus arteriosus	2.1	1.3	3.4
Venous anomalies			
Pulmonary veins	0.4	5.4	5.8
Vena cava	0.9	2.7	3.6
Ventricular septal defect			
Base	5.0	20.7	25.7
Elsewhere or multiple	0.5	1.2	1.7

1) main pulmonary artery, 2) pulmonary arterial segment, 3) pulmonary conus*, and 4) pulmonary arch. For convenience the last term will be used.

There are 3 basic types of congenital aberrations which may exist in an isolated form or more frequently in various combinations. The first type of aberration causes an obstruction to the flow of blood and would include stenosis, hypoplasia, atresia, and diaphragm formation. Usually when this type of anomaly exists, the chambers of the heart and great vessels proximal to the obstruction enlarge and hypertrophy. Sometimes a short segment of a great vessel distal to the obstruction may dilate and is called post-stenotic dilatation. Typically this dilatation occurs in the aorta and pulmonary arch. It is believed that this condition is more apt to occur when the obstruction is of the diaphragmatic type. The second major type of aberration is an abnormal communication, either between the cardiac chambers or between great vessel structures. This abnormal communication is called a shunt. The flow of blood is always from the high-pressure chamber to the low-pressure chamber. Typical examples are atrial septal defects and patent ductus arteriosus. The shunting defect is more apt to enlarge and hypertrophy that side of the heart and great vessels which carry the increased load of blood. Thus, in atrial septal defects the right heart generally is enlarged, and in patent ductus arteriosus the left heart is generally enlarged. The third basic type of anomaly would include aberrant structures. These structures may or may not be noted radiologically, and recognition is dependent upon the demonstration of structures with abnormal anatomical relationships such as are seen in transposition of the great vessels and in anomalies of the aortic arch.

As has been pointed out, the basic anomalies causing obstruction, abnormal communication, and aberration of structures usually exist in various combinations rather than in a pure isolated form. As if to complicate matters further in the study of congenital malformations of the heart and great vessels, it is not infrequent to find more than one complex of basic anomalies. Thus, one individual may have both coarctation of the aorta and patent ductus arteriosus[48].

It cannot be overemphasized that the radiologic examination is complementary to other methods and must never be taken out of context. The complete history and physical and laboratory findings must be carefully analyzed to gain full benefit from the radiologic examination. Also the relative accuracy of radiologic observations must be carefully assessed before a final radiologic opinion can be reached. For example, a statement of the general size of the heart is more reliable than a statement concerning the size of the individual chambers. Observations of the size of the pulmonary artery and conus are usually more accurate than observations concerning the hilar vessels.

Healy *et al.*[27] point out that a small left to right shunt with marked pulmonary hypertension has the same roentgenographic appearance as a large left to right shunt without marked pulmonary hypertension.

In this review no attempt will be made to discuss angiocardiography.

Definitions and Radiologic Findings. Aortic Arch Anomalies[16]. It will be recalled that the normal aortic arch is a derivative of the fourth left branchial arch. In its most primitive form both the right and left fourth branchial arches are retained and meet to form the dorsal aorta[37]. If this situation exists after birth, it forms a complete vascu-

* This phrase, pulmonary conus, should refer only to the outflow tract of the right ventricle. The conus cannot be visualized on the PA film.

lar ring surrounding the esophagus and trachea and may cause symptoms by compression of these organs. Either partial or complete atresia of portions of either arch results in many variations of the aortic ring. A common anomaly is the presence of a right aortic arch passing posteriorly to the esophagus and joining a left descending aorta. The left arch may be small and pass anterior to the trachea, forming a complete ring. Occasionally the ligamentum arteriosum or a patent ductus arteriosus forms the anterior branch of the ring[38]. Gross and Neuhauser[26] describe anterior compression of the trachea alone either by the innominate artery arising to the left of the trachea or by a left subclavian artery arising to the right of the trachea.

When atresia occurs embryologically between the right common carotid and right subclavian arteries, the latter originates from the dorsal aorta just distal to the left subclavian and passes upward and posterior to the esophagus.

The *roentgenologic findings* with aortic arch anomalies are usually compression and indentation of the posterolateral surface of the barium-filled esophagus. When iodized oil is instilled into the trachea, extrinsic compression may be noted on its anterior wall. Sometimes this phenomenon is seen without iodized oil by virtue of the normal contrast afforded by air in the trachea. Neuhauser[38] has described slight erosion of the anterior bodies of the thoracic vertebra contiguous to the anomalous vessel.

Atrial Septal Defect.[7,41,49]. A defect of the atrial septum can be due to a patent foramen ovale or to a patent ostium primum located below the foramen ovale. The flow of blood is usually from the left atrium to the right atrium, since the ventricular filling pressure is higher in the left atrium. The right heart is overloaded and consequently, depending on the size of the defect, the right atrium, right ventricle, pulmonary conus, pulmonary arch, and pulmonary vessels will show various degrees of enlargement.

In an analysis of 12 cases of atrial septal defects Healy, Dow, Sosman, and Dexter[28] found 11 had an increase in size of the main pulmonary artery and 9 showed increased activity. Nine cases had an increase in size of the hilar branches and 7 showed increased activity. Nine of the cases had prominence of the intrapulmonary vessels. In 9 the over-all heart size was increased. Eight had enlargement of the right ventricle. Only 4 had right atrial enlargement. The aorta appeared slightly small in 3. These authors reported 7 cases with left ventricular enlargement; however, autopsy proof is not available.

Biloculate and Triloculate Heart [22,35,42]. Cor biloculare represents a primitive arrest in the formation of the heart. There are a single atrium, a single ventricle, and a common atrio-ventricular valve. The pulmonary circulation may be by way of a patent ductus arteriosus if the main pulmonary artery is small or absent. Radiologically the findings are not distinctive. Shortly after birth the heart shows progressive enlargement and usually has a globular configuration if no pulmonary stenosis is present. If pulmonary stenosis is present, the heart remains small.

Cor triloculare may be divided into a 3-chambered heart with a double atrium and a 3-chambered heart with a double ventricle. The biatrial type is more common than the biventricular type. In an analysis of 21 autopsied cases of single ventricles seen at Johns Hopkins Hospital, Hosier has found the following groups[29]:

> *Group 1.* Four cases in which the aorta arose from the main chamber and the pulmonary artery arose from the rudimentary outlet chamber. Three of these cases had stenosis of the pulmonary artery.

Group 2. Eleven cases in which the aorta arose from a rudimentary outlet chamber. Three of the aortas had coarctation. The pulmonary arteries in these cases arose from the main chamber. Three of these pulmonary arteries had stenosis.

Group 3. Six cases. In these cases there was a resemblance to transposition of the great vessels. The aorta was the main vessel. The pulmonary arteries arose from the main chamber but behind the aorta. All these pulmonary arteries were stenotic or atretic.

Radiologically it is difficult to recognize a single ventricle. It is felt by some that the single ventricle exhibits a cardiac silhouette without character. The heart may extend below the diaphragm and on the AP view not much of the heart is to the right of the sternum. In the left anterior oblique view the heart is not prominent anteriorly. Sometimes the single ventricle has an appearance similar to that of tricuspid atresia. Electrocardiographic findings are extremely valuable. Either right or left predominance may be exhibited. If the pulmonary artery is small, the patient is decidedly cyanotic. On the other hand, if the aorta is hypoplastic, then the pulmonary artery is large and cyanosis may be at a minimum.

Coarctation of the Aorta. This entity is a congenital constriction of the aorta usually at or near the site of the ligamentum arteriosum. Usually coarctation is divided into the adult type and the infantile type. However, it is felt that this may be an arbitrary division. In the more common so-called adult type, the aorta is narrowed either at the site of the ligamentum arteriosum or just distal to it. In the majority of cases the left subclavian artery arises proximal to the stenotic segment. In the so-called infantile type the coarctation is often proximal to a patent ductus arteriosus. There are many variations with regard to the length and degree of coarctation. The prognosis in the infantile type is relatively poor because of the frequency of associated congenital defects. Because of the patent ductus arteriosus, collateral circulation does not develop.

The prognosis in the adult type is quite good and the patient usually reaches maturity and is relatively asymptomatic. There are 3 principle routes of collateral circulation: 1) by way of the internal mammary arteries, to branches of the subclavian arteries, into the epigastrics, and then to the external iliacs; 2) by way of the superior intercostal arteries, each branching from the subclavian artery, into the first intercostal artery which communicates with the descending aorta just distal to the stenosis; 3) or by way of the scapular arteries into the second intercostal artery. The pathognomonic clinical sign is a strong pulse in the arms and a weak pulse in the legs. Occasionally, if the coarctation is proximal to the left subclavian artery, the pulse in the right arm is strong and the pulse in the left arm is weak.

The *roentgenographic and fluoroscopic findings* are of considerable aid in confirming the diagnosis. The contour of the heart is usually characteristic of the hypertensive type with predominant enlargement of the left ventricle. The ascending aorta is enlarged and pulsates rather vigorously. In the PA position the aortic knob is frequently diminished in size. Also in this position a notch or indentation in the left side of the proximal descending aorta is frequently noted. If the summit of the arch can be clearly seen in the left anterior oblique position, a distinct notching with the acute angle pointing downward can be seen at the site of the ligamentum arteriosus. This finding is most likely due to a short fibrous ligament exerting tension on the arch downward and inward. This is also the

cause of the notching effect seen on the PA view. Stauffer and Rigler[43] have reported vigorous pulsation of the left subclavian artery observed fluoroscopically. A very characteristic, but not pathognomonic, radiologic finding is notching of the ribs. This notching becomes more apparent with age and is very rarely seen below the age of 10 years. Usually this notching effect is noted in the undersurface of the posterior 3rd, 4th, and 5th ribs lateral to the costal tubercle. In addition to these changes Kaner, Losch, and Green[33] have reported alterations in the pulps of the maxillary incisors, both deciduous and permanent. These pulps are enlarged and funnel shaped. The molar pulps are normal.

Coronary Artery, Aberrant[5,17]. In this anomaly the left coronary artery arises from the pulmonary artery. Shortly after birth the patient develops serious symptoms associatel with myocardial damage. It is thought that the low oxygen pressure is not so important as the low pressure in the pulmonary artery in the production of myocardial degeneration.

Roentgenographic and fluoroscopic examination reveals a large dilated left auricle and left ventricle. Very poor cardiac pulsations can be seen. Frequently pulmonary congestive changes are present. Roentgenologic findings are not characteristic and may resemble Fiedler's myocarditis, idiopathic enlargement of the heart, and occasionally Von Gierke's disease. The electrocardiogram is of great diagnostic value.

Dextrocardia. True dextrocardia should be distinguished from dextroposition of the heart. Dextroposition of the heart may result from agenesis of the right lung, severe deformities of the thoracic cage, and also atelectasis or pneumonectomy of the right lung.

Certain severe malformations of the heart, such as cor biloculare and malrotation, may result in dextroposition. These cases are extremely difficult to evaluate because of the loss of anatomical landmarks of the various chambers of the heart.

True dextrocardia is quite frequent. The over-all incidence is 1 case in every 10,000 of the general population[23]. There are 2 types: 1) the isolated dextrocardia which is a mirror image of the normal heart, and 2) dextrocardia with *situs inversus*. In dextrocardia the patient is usually asymptomatic and merely has the mirror image of the normal heart with or without a mirror image of the visceral structures. Fluoroscopy is the most certain way of diagnosing dextrocardia.

Ebstein's Disease[52]. Essentially this disease is due to the downward displacement of the tricuspid valve into the right ventricle. Instead of arising from the annulus fibrosus, which separates the right auricle from the right ventricle, the tricuspid valve arises in part from that ring and in part from the wall of the right ventricle. The anterior leaflet of the tricuspid valve is usually normally placed. The medial or septal leaflet is generally attached to the wall of the ventricular septum. The posterior leaflet is almost always malformed and not connected with the annulus fibrosus. The downward displacement of the tricuspid valve results in a small, poorly functioning right ventricle limited to the outflow tract and the pulmonary conus. The right ventricle above the displaced valve becomes incorporated into the right atrium. Occasionally an atrial septal defect or patent foramen ovale is present. The magnitude of symptoms depends upon 1) the degree of displacement of the tricuspid valve or how much functioning right ventricle remains, and 2) whether the malformed valve actually causes obstruction in the outflow tract resulting in pulmonary stenosis. The patient may be asymptomatic with minimal changes or have

severe circulatory embarrassment with severe changes. If symptoms do occur, arrhythmias, palpitation, and dyspnea are frequent. Cyanosis is usually not present unless a right to left shunt exists.

The *roentgenographic and fluoroscopic findings* are not distinctive. In proved cases the right side of the heart, especially the right atrium, may appear quite large. The pulmonary arch is small, a finding which aids in differentiating pure pulmonic stenosis. Fluoroscopically the right heart pulsates very quietly.

It is well to remember that these patients are susceptible to pulmonary tuberculosis. The electrocardiographic findings are helpful in that they show various arrhythmias, prolongation of the intraventricular conduction time, and occasionally right or left bundle branch block.

EISENMENGER'S COMPLEX. This condition is quite analogous to the tetralogy of Fallot except for the absence of stenosis of the pulmonary artery in Eisenmenger's complex. Both malformations have in common dextroposition of the aorta, high ventricular septal defect, and an enlarged right ventricle. While in Eisenmenger's complex there is no valvular or infundibular stenosis, pulmonary hypertension and peripheral pulmonary arteriosclerosis involving the media of the smaller arteries are present. Civin and Edwards[11] believe that the increased pulmonary resistance is retained from the fetal state and enhanced by arteriosclerotic changes after birth. Distinctive clinical features are the late onset of clubbing and cyanosis, usually post-adolescent. Hemoptysis is prone to occur in these patients.

The roentgenologic and fluoroscopic findings usually reveal slight enlargement of the heart which is slowly progressive. The right ventricle is frequently enlarged. A huge pulmonary arch and hilar vessels which usually pulsate are noted in the PA view. A large pulmonary conus is seen on the right anterior oblique projection. Radiologically the pattern resembles that of Lutembacher's syndrome. Proof of an overriding aorta is sufficient to rule out this latter entity.

LUTEMBACHER'S COMPLEX[21,34]. This condition is relatively rare and consists of an atrial septal defect and acquired or congenital mitral stenosis. There is no cyanosis.

The *roentgenographic and fluoroscopic* findings usually show an enlarged right heart. The right atrium is quite large. It is believed that the size of the left atrium is proportional to the degree of mitral stenosis and inversely proportional to the size of the atrial septal defect. An appreciation of the size of the left atrium is gained by observing the rounded displacement of the barium-filled lower esophagus in the right anterior oblique projection. The right ventricle is large and the left ventricle is quite small. The pulmonary conus is large. The pulmonary arch is frequently enlarged and saccular. The hilar and parenchymal vessels are prominent. The aorta is quite small.

There is considerable difficulty in differentiating Lutembacher's complex from a large atrial septal defect, Eisenmenger's complex, cor pulmonale, and sometimes pure pulmonic stenosis. If the pulmonary blood flow is very high, one may suspect that mitral stenosis is complicating an atrial septal defect. If no overriding of the aorta exists, then Eisenmenger's complex is ruled out. An overriding aorta can be established by supplementary procedures such as cardiac catheterization, angiocardiography, or the determination of a diminished circulation time.

PATENT DUCTUS ARTERIOSUS. In this condition there is a failure of involution of the fetal ductus arteriosus connecting the aorta and pulmonary artery.

After birth the flow is from the aorta to the pulmonary artery because of the higher pressure. Patent ductus may exist without causing any abnormal configuration of the heart or great vessels observable fluoroscopically or by roentgenogram. The diagnosis can then only be made with certainty by the characteristic continuous machinery murmur.

The majority of cases do present roentgenologic changes. The heart is larger than normal, particularly the left atrium and left ventricle. The pulmonary conus, pulmonary arch, and hilar arteries are often considerably larger than normal. Fluoroscopically there is an increase in pulsation of the left ventricle, the descending aorta, the aortic arch, and pulmonary conus. The proximal pulmonary artery may or may not pulsate excessively. The pattern of the peripheral pulmonary arteries appears normal. Rarely an aneurysm of the patent ductus arteriosus exists. Kaneidel[32] believes that it is possible for an aneurysm to be recognized as a smooth rounded pulsating shadow in the left hilar region in the site of the ductus. The trachea is frequently displaced forward and to the right. One should look for a thin shell of calcium which may be deposited in the aneurysmal wall. Calcification[39] has been noted in an occluded ductus presumably with thrombosis present. The same changes that occur with patent ductus arteriosus may exist with fenestration[13] of the aortic pulmonary septum and also with a high ventricular septal defect.

Pulmonary Arteriovenous Aneurysm or Fistula[51]. While this entity is not strictly a congenital malformation of the heart or great vessels, it is included because it may be confused with cyanotic heart disease. There are anomalous connections between the pulmonary arteries and pulmonary veins. The blood is short-circuited through the lungs without being oxygenated, thus causing cyanosis and polycythemia. The condition may be familial. It is a congenital aberration and occasionally it is associated with congenital anomalies of the heart such as those of the Eisenmenger type. Frequently this condition has numerous fistulae in both lungs and is not amenable to surgery. However, when it is single, it can be readily approached surgically and cured.

The diagnosis can be made radiologically in certain instances when a well-defined lesion is noted within the parenchyma of the lung. A serpiginous or circinate vascular lesion can be seen. Sometimes, particularly with a laminogram, afferent or efferent vessels may be identified. The size of the lesion varies with changes in intrapulmonary pressure as produced by the Valsalva test on deep inspiration and the Muller test on forced expiration against the closed glottis. Angiocardiography can give definitive findings. The heart is usually normal but may be slightly enlarged.

Pure Pulmonic Stenosis[6,15,19,40,50]. In this entity there is a single stenotic lesion in or near the valve of the pulmonary artery. Commonly the cusps are congenitally fused to form a diaphragm with a small opening. Four percent of the stenoses of cases operated upon at Johns Hopkins Hospital were in the infundibular region. When a diaphragm is present, Brock[6] has devised an operation to separate the fused cusps and thereby alleviate the obstruction. Cyanosis is not a striking feature in pure pulmonic stenosis. It is noticeable with respiratory stress such as crying and coughing.

The roentgenographic and fluoroscopic findings show an enlarged heart, particularly on the right side, including the atrium and right ventricle and a large pulsating superior vena cava. The pulmonary conus is larger than normal as viewed in the right anterior oblique

projection. In the posterior anterior view there is no concavity in the left side of the cardiac waist, a useful point differentiating tetralogy of Fallot. Isolated pulmonic stenosis shows fullness of the pulmonary arch due to poststenotic dilatation. The peripheral pulmonary vessels are small and the lung fields are strikingly clear. The apex of the heart is lifted by the hypertrophied right ventricle.

It is exceedingly difficult to be certain of the relative size of the right and left ventricles. In the left anterior oblique projection Dammann[14] suspects that an enlarged left ventricle causes a bulging posterior border with a rounded postero-inferior ventricular apex. A large right ventricle displaces the left ventricle posteriorly and possibly causes a straight posterior border with a sharply angulated postero-inferior apex.

Tetralogy of Fallot[15]. This common malformation exhibits the tetrad described by Fallot, namely, 1) stenosis of the pulmonary infundibulum, 2) dextroposition of the aorta, 3) high ventricular septal defect, and 4) hypertrophy of the right ventricle. These patients are all cyanotic and frequently live to maturity. This group of patients benefits greatly by the shunting of systemic blood into the pulmonary artery accomplished by the Blalock–Taussig or Potts surgical anastomosis.

The *roentgenographic and fluoroscopic findings* are as follows: The heart is usually not enlarged. The apex of the heart is elevated and appears rounded, likened to a wooden shoe or a sheep's nose. This elevation is caused by the hypertrophy of the right ventricle. The right auricle and superior vena cava are quite full but not so much as in pure pulmonic stenosis. The pulmonary conus in the right anterior oblique projection is small and the contour of the heart exhibits a concavity in this region. On the PA projection there is a concavity in the cardiac waist due to the stenosis of the pulmonary artery. The hilar arteries exhibit an abnormal pattern, difficult to describe. There appear to be quite numerous blood vessels; however, they are smaller in caliber than the normal pulmonary trunks and appear more like a vascular matting. The peripheral lungs show a diminution of the vascular markings resembling the clarity seen in pure pulmonic stenosis. If a high degree of pulmonary stenosis is present, evidence of an increase in the collateral circulation of the bronchial artery supply to the lungs can sometimes be seen. Campbell[8] has noted a blurring of the under surface of the aortic arch on the left anterior oblique projection due to the presence of numerous small bronchial vessels. The hilar patterns are also remarkable, for the normal full hilar pulmonary arteries with a gradual tapering cannot be distinguished; this pattern is replaced by a less orderly patchwork of finer vessels. Approximately 20% to 25% of the patients have a right aortic arch. The position of the arch is important to determine because the Blalock–Taussig operation is done on the side opposite to the aortic arch. It is relatively easy to determine the right aortic arch by fluoroscopy. A swallow of barium is given and the indentation of the esophagus by the aortic arch is noted to be on the right rather than normally on the left. The proximal descending aorta can often be seen slightly to the right of the spine, and the superior vena cava is usually displaced to the right before its entry into the right auricle. The right aortic arch is the mirror image of the normal left aortic arch. The trachea is displaced slightly to the left.

Transposition of the Great Vessels[9,18]. This is a severe congenital malformation in which the aorta arises from the right ventricle and the pulmonary artery arises from the left

ventricle. The condition is incompatible with life unless there is a concomitant atrial septal defect, a ventricular septal defect, or a patent ductus arteriosus. These defects allow mixing of the blood between the right and left hearts. The patients are definitely cyanotic and as a rule do not fare very well.

Radiologically the heart is quite large, both the right and left hearts being involved. All the individual chambers are enlarged. The most distinctive finding in infancy is the narrowing of the vascular pedicle at the base of the heart in the PA view. This is due to the fact that the aorta lies anteriorly and the pulmonary artery is posterior to the origin of the aorta. In the left anterior oblique projection both vessels are seen *en face* and the vascular pedicle is considerably wider. The hilar vessels are much more prominent than in the tetralogy of Fallot, and the peripheral pulmonary vessels are of good size, so that the lungs do not appear avascular. In older children the great vessels dilate so that the radiologic pattern is not so characteristic. Confusion with Eisenmenger's complex may arise, but can usually be resolved on clinical grounds.

A modification of the transposition has been found by Taussig and Bing and is sometimes referred to as the Taussig–Bing syndrome[47]. The prognosis of this modification is favorable. It is essentially an overriding of the pulmonary artery so that it straddles the septum between the right and left ventricles. When a transposition is suspected radiologically, the Taussig–Bing syndrome may be suggested by the fact that the pulmonary conus and artery are more normally placed than in the true transposition. The vascular pedicle is not so narrow in the PA position and the pedicle is not so wide in the left anterior oblique position.

Tricuspid Atresia. This is also known as tricuspid stenosis and underdeveloped right ventricle. The essential aberration is the narrowing or absence of the tricuspid ring and various degrees of hypoplasia of the right ventricle with stenosis of the pulmonary artery. Usually there is a gross defect in the artrial septum which allows blood to enter the left heart, whence it may reach the pulmonary circulation through a ventricular septal defect or a patent ductus arteriosus. Cyanosis is usually persistent and intense. The electrocardiogram is quite distinctive because this anomaly is the only one of the cyanotic type that shows left axis deviation (except for a few single ventricles).

Roentgenographic and fluoroscopic examination shows a small right ventricle in all projections, particularly in the left anterior oblique view. The superior vena cava is enlarged. The left contour of the heart in the PA view resembles the tetralogy of Fallot, in that there is absence of the conus and pulmonary arch which causes a concavity in the cardiac waist. However, the apex extends down below the dome of the diaphragm. The rudimentary right ventricle often fills in the dorsum of the boot, giving it a rather "fat" appearance. The hilar arteries and peripheral pulmonary arteries are diminished in size. The lungs appear unusually clear. The left ventricle is enlarged, as is demonstrated by the lack of clearance of the spine in the left anterior oblique position. The right atrium is enlarged but may not appear so because of the diminutive right ventricle.

Truncus Arteriosus[46]. This aberration basically is a single large arterial trunk receiving the outflow of both the right and left ventricles. Embryologically it is an arrest in the septation of the truncus before the division of the truncus into the aorta and pulmonary arteries. The so-called pseudo-truncus

is thought to be a more primitive form with the lungs supplied by the bronchial arteries. Vestigial pulmonary arteries are present but do not connect with the heart.

Clinically there is minimal cyanosis when large pulmonary branches arise from the ascending aorta and there is more intense cyanosis when the circulation of the lungs is derived from the bronchial arteries.

The *roentgenographic and fluoroscopic findings* are as follows. The superior vena cava is not dilated. The right atrium is prominent. The right ventricle is enlarged. The left atrium is usually normal in size and the left ventricle is considerably enlarged. A single large vessel arises from the base of the heart to form the truncus. The pulmonary artery can occasionally be seen arising from the single large truncus in a much higher than normal position. When the bronchial arteries supply the lungs, no pulmonary trunks are visualized. Instead there is an absence of the hilar comma shadows and an interlacing network of small blood vessels in the hilar regions. Usually the superior bronchial arteries are quite well developed and cause the undersurface of the aortic arch to be hazy, which is particularly well seen in the left anterior oblique position[8]. When a swallow of barium is given the bronchial arteries may indent the surface of the barium-filled esophagus. The peripheral lungs are unusually clear when this situation prevails. Occasionally the pulmonary artery can be seen as a single large vessel arising in a high position. Characteristically the entire heart is enlarged and has a prominent shelf effect projecting to the right at the base of the truncus, best seen in the left anterior oblique view. After infancy the contour of the heart may resemble closely the tetralogy of Fallot.

VENOUS ANOMALIES[2,10,31]. There are 2 main types: 1) aberrant pulmonary veins opening into the superior vena cava or right atrium, and 2) aberrant right or left superior vena cava opening into the left atrium. A single anomalous pulmonary vein is an infrequent aberration and does not cause cyanosis. It simulates closely a small atrial septal defect. The superior vena cava is slightly enlarged, and the right atrium and right ventricle also appear enlarged due to the overloading of the right heart.

The *roentgenographic and fluoroscopic findings* are identical with the atrial septal defect. The differentiation can be made by angiocardiography or cardiac catheterization. Occasionally on the plain films the aberrant vein can be recognized as a sickle-shaped shadow adjacent to the right heart border.

When all pulmonary veins enter the superior vena cava, right auricle, or coronary sinuses, a very unfavorable situation exists. In order to live, the patient must have a patent foramen ovale or atrial septal defect. Even with this defect the heart shows marked progressive enlargement confined to the right side. Angiocardiography exhibits marked vascularity and recirculation of dye in the right heart. Eventually the patient dies of cardiac failure and exhibits cyanosis terminally.

Anomalous opening of the vena cava into the left auricle may produce cyanosis. The *roentgenographic and fluoroscopic* findings are as follows. The superior vena cava may be dilated or abnormally placed. Occasionally a dilated left-sided superior vena cava is noted. The right atrium and ventricle appear normal or slightly smaller than normal. The left atrium is enlarged as evidenced by the concavity of the barium-filled esophagus in the right anterior oblique view. Again angiocardiography may be necessary for a definitive anatomical demonstration of the aberrant vein.

VENTRICULAR SEPTAL DEFECT (MALADIE DE ROGER)[36]. A ventricular septal defect is characterized by a simple small perforation in the wall of the ventricular septum. The location and size of the defect vary considerably. No cyanosis is present in this condition because the flow of blood is from the high-pressure left ventricular chamber to the lower-pressure right ventricular chamber. Usually the opening is small and a characteristic finding is a harsh systolic murmur over the precordium. Often this is the only clinical finding.

The *roentgenologic and fluoroscopic findings*, for the most part, reveal a heart perfectly normal in size, shape, and configuration. In cases in which there is a high, large ventricular septal defect, the anomaly resembles conditions found in a large patent ductus. A large volume of blood may be forced from the left ventricle into the pulmonary artery and cause dilatation of the pulmonary artery. As with a patent ductus, the strain is on the left heart and there may be dilatation of the left atrium and left ventricle.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

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Relationship between Hypothalamic Temperature and Thermoregulatory Effectors in the Unanesthetized Cat. R. E. FORSTER, II, M.D., and T. B. FERGUSON, M.D. (Dept. of Physiol., Harvard Med. Sch., Boston, Mass.). In order to estimate the importance and limits of the control of thermoregulation by the hypothalamic temperature, a small thermistor on the end of a fine glass needle was permanently affixed in the hypothalamus of 8 cats. The animals had recovered several days following operation and were maintained 6 to 67 days. Brain damage was minimal as judged both by physiological tests of temperature regulation and by microscopic sections on 3 animals. Hypothalamic temperature, as indicated by the thermistor, was from 0.52 above to 1.2° C. below rectal temperature and showed many irregular nonrhythmic variations as great as 0.5° C. without obvious cause. Deep peritoneal sodium pentobarbital anesthesia eliminated the small variations in hypothalamic temperature and rendered the animals relatively poikilothermic, whereas light anesthesia had no consistent effect. In general, rest tended to lower hypothalamic temperature, exercise or excitement to increase it. In 5 cats, panting, whether produced by radiant heaters or by hot air, occurred whenever the hypothalamic temperature rose above a "threshold" range. When the hypothalamic temperature dropped below this range following the intragastric introduction of cold water through a nasal catheter in one of these animals, panting ceased in spite of a continued external heat load. Two animals showed no relationship between hypothalamic temperature and panting and were considered "reflex" panters. In 5 cats tested, thermoregulatory vasodilation and vasoconstriction usually occurred without any apparent causal relationship to hypothalamic temperature. These data are felt to be consistent with the hypothesis that in most unanesthetized cats, panting is primarily controlled by hypothalamic temperature, while thermoregulatory vasomotor reactions, within the limits tested, are not.

Observations on the (*in Vivo*) Action of a New Lipotropic Fraction of the Pancreas. J. E. RHOADS, M.D., OSCAR LIBORO, M.D., SAMUEL FOX, M.D., PAUL GYÖRGY, M.D., and T. E. MACHELLA, M.D. (Harrison Dept. of Surg. Res., School of Med., Univ. of Penna., and the Surg. Clinic, the Nutritional Serv. of the Dept. of Pediat., and the Gastro-Intestinal Sect. of the Dept. of Med., Hosp. of Univ. of Penna., Phila.). A pancreatic extract described by Bosshardt, Ciereszko, and Barnes was tested in the depancreatized dog and was usually effective in doses of 60 mg. per day in preventing fatty infiltration of the liver as compared with controls (difference significant). The impression was gained that it was less effective in those animals that consumed little or none of the artificial diet than in those that ate reasonably well. Its effectiveness was destroyed by three minutes' boiling (statistical significance borderline). These observations were interpreted as suggesting but not proving that the material acted as an enzyme.

Observations on the (*in Vitro*) Action of a New Lipotropic Fraction of the Pancreas. M. L. HAANES, M.D., and PAUL GYÖRGY, M.D. (Nutritional Serv. of the Hosp. of the Univ. of Penna.). A new potent lipotropic fraction has been separated from pancreas (Fraction A-1)* which is effective only orally in depancreatized dogs. It has no action in the dietary induced fatty liver of rats or when given parenterally (actions attributed to the fraction Lipocaic prepared by Dragstedt), but resembles the action of fraction C-27 (prepared by Chaikoff), which is attributed to the presence of proteolytic enzymes. Initial tests of fraction A-1 failed to show proteolytic activity. However, *in vivo* studies were strongly suggestive of the presence of enzymes. Further *in vitro* studies were therefore performed to clarify these observations.

Proteolytic activity was studied, using a pepsin digest of casein as the substrate, and measuring digestion by a microbiological assay for methionine. Fraction A-1 was inactive alone, but showed proteolytic activity when duodenal juice (either hog duodenal substance or juice from the depancreatized dog) was added to the substrate. Further analysis of fraction A-1 resulted in the separation of an active proteolytic enzyme and an enzyme inhibitor which supressed its action except in the presence of duodenal juice. These substances were tentatively identified as trypsin and trypsin inhibitor, although the presence of small amounts of other known proteolytic enzymes was not ruled out. The factor in duodenal juice which suppressed the inhibitor is postulated to be enterokinase, since it is heat labile and is non-proteolytic. This action of enterokinase has not previously been described.

It is concluded that fraction A-1 contains an active proteolytic enzyme which is masked by an enzyme inhibitor. The effect of the inhibitor is suppressed in the intestinal tract by a substance presumed to be enterokinase. It acts by releasing choline precursors, such as methionine, from ingested protein, which then exert a direct lipotropic action in the liver.

Integrated Teaching in Basic Sciences: Report on Five Years of Experience. J. H. COMROE, JR., M.D., D. L. DRABKIN, M.D., W. E. EHRICH, M.D., J. A. FLICK, M.D., S. S. KETY, M.D., and W. M. KROGMAN, M.D. (Grad. Sch. Med., Univ. of Penna., Phila.). A report was given upon the experience of the basic science faculty in the Graduate School of Medicine with the program for integrated basic science teaching conducted in that school for the last 5 years. The general arrangement of the schedule is on an organ system basis, in which physiology, physiological chemistry, pathology, bacteriology, immunology, pharmacology, and physical anthropology are presented together as they pertain in turn to the various organ systems of the body. The change from the usual method of presenting the basic sciences as separate unrelated courses in favor of this integrated course has enabled the physician-students to see clearly the integration of the various basic sciences with each other and their correlation with clinical medicine. It is believed that modification of this plan can be applied to undergraduate teaching if the chief requirements for integrated teaching are fulfilled; these are wholehearted enthusiasm on the part of the faculty to participate in this new educational experiment, willingness to ignore small differences of opinion in the interest of harmony and co-operation, and genuine interest in the teaching problems of medicine.

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BOOK REVIEWS AND NOTICES

THE CARE AND BREEDING OF LABORATORY ANIMALS. Edited by EDMOND J. FARRIS, The Wistar Institute of Anatomy and Biology, and 15 contributors. Pp. 515; 67 ills. New York: John Wiley & Sons, 1950. Price, $8.00.

As the Editor states, species included in this book were selected on the basis of their frequency of use in research laboratories today. Ten species of mammals are considered. There is a chapter on the common fowl, and a chapter each on reptiles, amphibia, fish, and *Drosophila*. One chapter deals with the control of laboratory pests and parasites.

The book should prove especially useful to research laboratories having occasion to work with a variety of animals. C. B.

FUNCTIONAL ANATOMY OF THE LIMBS AND BACK. By W. HENRY HOLLINSHEAD, A.B., M.S., Ph.D., Head, Sect. of Anatomy, Mayo Clin.; Prof. of Anatomy Mayo Found., Univ. of Minnesota. Pp. 341; 122 ills. Phila.: W. B. Saunders, 1951. Price, $6.00.

THE Author is to be congratulated for this "down to earth" coverage of two far-reaching basic sciences. He has condensed considerable anatomy and physiology in this volume. It naturally follows that the subjects are reduced to their simplest levels. As such, the book will be useful to early medical students, biology students, physiotherapists, and possibly nurses. The illustrations, while not copious, are excellent in that they are clear-cut, readily understood diagrams. A. S.

THE LOW FAT, LOW CHOLESTEROL DIET. By E. VIRGINIA DOBBIN, HELEN F. GOFMAN, M.D., HELEN C. JONES, LENORE LYON, and CLARA-BETH YOUNG. Pp. 371. Garden City, N. Y.: Doubleday, 1951. Price, $3.45.

THE rapidly increasing body of evidence tending to incriminate disturbed lipid metabolism in the etiology of atherosclerosis has led to a great interest in the means available for providing a nutritionally adequate and reasonably pleasant low fat, low cholesterol diet. This volume, written by two dieticians, a physician and housewife, a home economist, and another housewife, provides in a remarkably practical manner the information needed by the physician prescribing the diet and by the patient or the patient's wife. Recipes are supplied in abundance and with complete details as to the preparation of the various foods. In each diet presented the authors have been careful to determine that nutritional requirements have been adequately provided. This book meets a very real need in the medical practice of today. T. D.

PLASMA PROTEINS. Edited by JOHN B. YOUMANS, M.D., Dean and Prof. of Med., Vanderbilt Univ., Nashville, Tenn. Vol. 2, Symposia on Nutrition, Robert Gould Found. Pp. 352; figs. Springfield, Ill.: Charles C Thomas, 1950. Price, $6.50.

THIS volume consists of 18 papers delivered at a Symposium on Plasma Proteins held under the auspices of the University of Illinois in the fall of 1949. The papers cover all aspects of the plasma proteins ranging from biochemical to clinical. The book is of extreme value since it makes readily accessible a great volume of research material which would otherwise remain scattered through the literature. N. G.

A GUIDE TO MEDICINE. By IVO GEIKIE-COBB, M.D., with Special Articles by Various Contributors. Pp. 416. New York: Duell, Sloan & Pearce, 1951. Price, $5.00.

THE apparent intention of this book is to serve as something between a medical dictionary and an encyclopedia. It is said to be "for professional and home use". It is impossible, however, to see how it can contribute anything of value to the physician or to the medical student who will desire either the far more extensive word listing of the medical dictionary or the much more detailed descriptions of the standard medical texts, depending on the need of the moment. For the layman the book may have some value, but there are a number of "definitions" which would leave such a reader confused, and harm might be done. The discussion of hypotension may be cited as an example of this. The implication here is that it is important, regardless of circumstances, to raise a low blood pressure. We are told that it is important to "insist on adequate rest, to give a full diet, with alcohol (if indicated), and to amplify the general treatment by tonics"! Some of the contributions (such as the 4-page discussion of the antibiotics by Dr. Fleming) are, however, excellent. T. D.

NEW BOOKS

Medical Care for Seamen. The Origin of Public Medical Service in the United States. By ROBERT STRAUS. With a Preface by L. A. Scheele, Surgeon General, U.S.P.H.S. Pp. 165. New Haven: Yale Univ. Press, 1950. Price, $3.75.

THE present far-reaching Federal care of the public's health is, as many know, an outgrowth from the Marine Hospital Service, which was derived in 1870 from the Marine Hospital Fund (Act of 1798). This book, based on the Author's Yale doctoral dissertation of 1947, traces the growth of the institution through other changes of name, the "Public Health and Marine Hospital Service" (1902) to the "Public Health Service" (1912). However, public health is here considered entirely in its relation to the medical care of seamen. Moreover, considering its subtitle and that it is the opener of a new series on Merchant Seamen Studies, it has a disappointingly small amount of historical narration, and that none too well arranged. Of the 2 specific purposes stated in the Introduction, the conditions under which the federal government entered medical care are well enough described; but the more difficult indications for future trends are indeed scanty. The 10 pages of Chapter 9 are welcome exceptions, though even these do not include the more recent items of the expanded scope of public health. The arguments in the last 2 pages of the book will undoubtedly be rejected in many quarters and are not strengthened when the Author "assumes his conclusions".

E. K.

Recent Advances in Nutrition, with *Particular Reference to Protein Metabolism.* By PAUL R. CANNON, Ph.D., M.D., Chairman Dept. of Pathol., Univ. of Chicago. (Porter Lectures, Series 14). Pp. 74. Lawrence, Kansas: Univ. of Kansas Press, 1950. Price, $2.00.

THIS series of Porter Lectures summarizes the valuable experimental observations of Dr. Cannon and his staff upon the relative protein values of various foodstuffs. In particular the role of the essential amino acids for maintaining protein reserves and resistance to infection are clearly defined. The medical implications of these observations are assessed; some of the facets of protein nutrition still to be explored are discussed. H. V.

Protein and Amino Acid Requirements of Mammals. Edited by ANTHONY A. ALBANESE, Nutrition Res. Lab., St. Luke's Hosp., New York, N.Y. Pp. 155. New York: Academic Press, 1950. Price, $4.00.

INVESTIGATORS from five laboratories combine to produce this review of current knowledge of protein and amino acid nutrition, and of the techniques employed in these evaluations. The collaborators and their topics are: H. H. Mitchell, Some Species and Age Differences in Amino Acid Requirements; D. V. Frost, Methods of Measuring the Nutritive Value of Protein Hydrolysates and Amino Acid Mixtures; R. H. Silber and C. C. Porter, The Laboratory Evaluation of Amino Acid Mixtures and Protein Hydrolysates; B. F. Chow, Dietary Protein and Synthesis of Tissue Proteins; and A. A. Albanese, The Protein and Amino Acid Requirements of Man. H. V.

NEW EDITIONS

Pharmacology and Therapeutics. By ARTHUR GROLLMAN, Southwestern Med. Sch. of Univ. of Texas. 13th ed., rev. Pp. 828; 104 ills. Phila.: Lea and Febiger, 1951. Price, $10.00.

THIS textbook for "students and practitioners of medicine" is essentially an extensive revision of the 13th edition of "Cushny's Pharmacology and Therapeutics" by Drs. Grollman and Slaughter. The arrangement of material has been changed. There are general discussions introducing such groups of drugs as chemotherapeutic agents, anti-epileptics, and autonomic drugs. All topics have been revised and much of the material rewritten. Important new therapeutic agents, for example, aureomycin, terramycin, vitamin B_{12}, and histamine-antagonizing agents, have been added. There are about 40 new figures. The appendix contains a useful concise section on prescription writing. The alterations have been accomplished by judicious shortening of previous material without increasing the length of the text. D. C.

Psychotherapy. By PAUL SCHILDER, M.D., formerly Clin. Dir., Bellevue Hosp., Psychiat. Div., and Res. Prof. of Psychiatry. Revised by LAURETTA BENDER, M.D., Assoc. Prof. of Psychiatry, New York Univ. Coll. of Med., and Senior Psychiatrist, Bellevue Hosp. 2nd rev. ed. Pp. 396. New York: W. W. Norton, 1951. Price, $5.00.

THE 1st edition of this classic textbook appeared in 1938 and was extremely well received. Dr. Bender, with a long association with Dr. Schilder as colleague and wife, has added footnotes to the 1st edition and has expanded some of the chapters by including several of Dr. Schilder's papers. This makes an even richer experience for anyone interested in the subject of psychotherapy. Some of the book is primarily for the psychiatrist, but there are many chapters which will interest any physician who is concerned with the emotional life of his patients. Dr. Schilder was a most penetrating and stimulating observer with an original presentation of the subject of psychotherapy. The bibliography and index are extensive. O. E.

The Amino Acid Composition of Proteins and Foods. By RICHARD J. BLOCK, Ph.D., New York Medical College, and DIANA BOLLING, B.S. 2d ed. Pp. 601; 45 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $10.50.

THIS valuable reference book has been extensively revised and enlarged to include new developments in amino acid chemistry since 1945. The number of pages and references has been nearly doubled. Among the numerous additions are sections on the chemical determination of methionine and cystine, the electrolytic separation of amino acids, chromatographic methods for separation and determination of amino acids, and microbiological and enzymatic methods for amino acid determination. The invaluable tables (230 of them) that gather together all available data on the concentration of amino acids in various plant and animal tissues have been retained, although they have been enlarged to include more data and have been revised in terms of gm. of nitrogen rather than %. The Authors' comments on each method discussed should prove helpful to any worker beginning amino acid determinations.

M. B.